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Archives of Internal Medicine

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CAN THE GALLBLADDER EMPTY THROUGH DUODENAL BILIARY DRAINAGE? IS THE GALLBLADDER THE SOURCE OF "B" BILE?

A CHOLECYSTOGRAPHIC STUDY OF BILIARY DRAINAGE *

B. B. VINCENT LYON, M.D.
PHILADELPHIA

In the discussion that followed a program on the diagnosis of and treatment for disease of the biliary tract at the annual meeting of the American Gastro-Enterological Association in May, 1927, Dr. Louis Gregory Cole pointed out that there was a great difference of opinion as to the merits or demerits of drainage of the biliary tract by means of the duodenal tube and that it was still a matter of dispute as to whether it was possible to evacuate the liquid contents of the gallbladder by any manner of intraduodenal stimulation. He thus subjected to recriticism the source of the so-called "B" bile. He suggested the desirability of studying a series of patients by oral cholecystography and drainage of bile by the duodenal tube to see whether the shadow of the dye-filled gallbladder could be made to disappear or be reduced in size; this experiment was to be further controlled by a meal rich in fat, and Dr. Cole offered his services for such a study with the purpose of settling this aspect of a controversial topic.

I pointed out to Dr. Cole that studies of this kind had already been made in both this country and abroad, some of which had been published. Nevertheless, arrangements were completed to investigate with Dr. Cole a series of patients in Philadelphia on May 9, 10 and 11, 1927. Through the courtesy of Prof. Willis F. Manges, the facilities of his x-ray laboratory at the Jefferson Hospital were placed at Dr. Cole's disposal.

Further to control the chief point of the investigation as to whether the gallbladder could be made to empty its dye rich bile by the duodenal tube and further to settle the question as to the source of the "B" bile, it was proposed to estimate quantitatively the iodine content of the "B" and "C" biles, and to Dr. G. A. Williams of the staff of Prof. Winthrow Morse was assigned this task:

* Submitted for publication, Sept. 21, 1928.

* Read before the American Gastro-Enterological Association, Washington, D. C., May, 1928.

SELECTION OF PATIENTS AND PROCEDURE

For this study nineteen patients were assembled, all of whom were suspected of having, or were known to have, some form of disease of the biliary tract with more or less involvement of the gallbladder. Six were women between the ages of 30 and 60 (average age, 49), and thirteen were men between the ages of 26 and 53 (average age, 40). Seven patients were studied on May 9, six on May 10 and six on May 11.

For the first day's study, the seven patients were given a dinner rich in fat at 6:30 on the previous night, and at 9:30 they commenced to take at fifteen minute intervals two keratinized capsules containing 0.4 Gm. of sodium tetraiodophenolphthalein and one capsule containing 0.3 Gm. of sodium bicarbonate until eight and four capsules, respectively, had been taken. The eight capsules of the dye represented a total dosage of 3.5 Gm. for an average person weighing from 145 to 160 pounds (65.8 to 72.6 Kg.). At Dr. Cole's request, these capsules and directions for taking them were furnished by Dr. William H. Stewart of New York.

For the patients studied on May 10 and 11, Dr. Manges furnished eight capsules each containing 0.4 Gm. of a brand of tetiothalein sodium-N.N.R. or a total dosage of 3.5 Gm.: two of these capsules were taken at fifteen minute intervals commencing at 9:30 p. m., three hours after a meal rich in fats. All patients reported at the Jefferson Hospital Clinic at 8 o'clock the following morning without having had further food or drink since the previous night at 6:30.

Freshly sterilized duodenal tubes with individual syringes and glassware were used, and the drainages were conducted by Misses Gledhill and LeVan, under the supervision of Drs. Lyon and Swalm. The duodenal tube was passed, the fasting residuum was removed, the stomach lavaged and the tube allowed to pass into the duodenum in the usual manner, and stimulations were given with from 30 to 75 cc. of magnesium sulphate solution (33 per cent volumetric), from 50 to 100 cc. of a 10 per cent solution of peptone and 30 cc. of olive oil. In most cases only one of these stimulants was used; in other cases, all three were given. When the tube was considered to have reached the duodenum, the patient was sent to the x-ray department, and under the supervision of Dr. Cole and Mr. Kelly a first film was made, representing as nearly as possible, a twelve hour exposure of the region of the gallbladder following the use of the dye.[1] The patients were then returned to the drainage room and biliary drainage continued until the sixteenth hour period, when the second x-ray film was made; following this the duodenal tube was withdrawn and the patient sent out for a luncheon rich in fats; the third film was made, as nearly as possible, one hour later. The luncheon consisted of two poached eggs, two slices of bacon, two slices of bread and butter and one glass of half milk and half cream.

On the second and third day's study, the procedure was changed to this extent: drainage was continued until an additional picture was made at the eighteenth hour period before the meal rich in fats and a fourth picture one hour later. While still wet the films were given a preliminary reading by Drs. Cole and Lyon, and the following day and subsequently were given final readings individually

1. In several patients, from whom bile was freely drained before the first film was made, it was found that after they walked a distance of nearly 100 yards to the x-ray room the tube had been withdrawn from 2 to 5 inches (5 to 12.7 cm.), and the x-ray showed the tip at the pylorus or within the stomach. To prevent this, the patients were subsequently taken to the x-ray room in a wheel chair.

by Drs. Cole and Manges. The degree of density of the shadow of the dye was graded upward from 1 to 4. In this report the readings of Dr. Cole have been used.

All "B" and "C" biles drained were sent under code numbers to the chemical department for estimation of iodine content. The following method was used for determining the amount of iodine: Three cubic centimeters of bile was placed in a nickel crucible with 1 cc. of concentrated sodium hydroxide solution and 0.5 Gm. of potassium nitrate, and the mixture evaporated to dryness on the electric hot plate. The crucible was then heated over a small flame until the residue melted, and then the molten mass heated to redness for thirty seconds. After cooling, the fused mass was dissolved in 20 cc. of distilled water. The solution was made distinctly acid to litmus by the addition of tenth-normal hydrochloric acid. In most cases, 3 cc. of acid sufficed. Five cubic centimeters of chloroform was then added, and the whole shaken vigorously in order to extract the iodine. The supernatant liquid was decanted from the chloroform and the colored chloroform solution of iodine titrated against five hundredth-normal sodium thiosulphate in the usual manner with starch as the indicator. The iodine content was reported in terms of milligrams of iodine per cubic centimeter of bile.

This study was designed to prove two points: (1) that the gallbladder can empty its liquid contents following intraduodenal stimulation, and (2) that the gallbladder represents the source of the "B" bile.

Before the results are reported, it is desirable that a short review of certain previous work be placed in evidence. Some of this is furnished by surgical observation of the gallbladder, some by experimental work on various animals, and some by clinical investigations similar to the present study.

The general principles which we originally and subsequently advanced [2] in regard to biliary drainage have been confirmed by a large

2. Lyon, B. B. Vincent: Diagnosis and Treatment of Diseases of the Gallbladder and Biliary Ducts, J. A. M. A. **73**:980 (Sept.) 1919; Some Aspects of the Diagnosis and Treatment of Cholecystitis and Cholelithiasis, M. Clin. N. Amer. **3**:1253 (March) 1920; The Treatment of Catarrhal Jaundice by a Rational, Direct and Effective Method, Am. J. M. Sc. **159**:503 (April) 1920; Need of Early Diagnosis and Treatment of Biliary Tract, New York M. J. **112**:23 (July 3) 1920; **112**:56 (July 10) 1920; Can the Gallbladder, Biliary Ducts and Liver be Medically Drained? Am. J. M. Sc. **160**:575 (Oct.) 1920. Lyon, B. B. V.; Bartle, M. J.; Ellison, R. T., and Richardson, R.: Discussion of the Treatment of a Case of Chronic Arthritis, with Lambliasis, by Duodenal Biliary Drainage, M. Clin. N. Amer. **4**:1153 (Jan.) 1921. Lyon, B. B. V.; Bartle, H. J., and Ellison, R. T.: Some Lessons Learned from Duodenobiliary Drainage, Am. J. M. Sc. **162**:60 (Jan.) 1922; **162**:223 (Feb.) 1922. Lyon, B. B. V.: A Reply to Certain Antagonistic Criticism of Nonsurgical Biliary Tract Drainage, New York M. J. **115**:269 (March) 1922; **115**:456 (April) 1922. A Brief Consideration of Nonsurgical Gall Tract Drainage as an Aid to the Surgeon, Penn. State M. J. **25**:392 (March) 1922; Nonsurgical Drainage of the Biliary Tract, Philadelphia, Lea & Febiger, 1923; The Value of Nonsurgical Drainage of the Biliary Tract as a Therapeutic Measure, Med. C. N. Amer. **8**:803 (Nov.) 1924; What Shall We Do with and for Our Cases of Gall Tract Disease? Therap. Gaz. **40**: 766 and 854 (Nov. and Dec.) 1924; Lyon, B. B. V., and Swalm, W. A.: Giardiasis: Its Frequency, Recognition, Treatment and Certain Clinical Factors, Am. J. M. Sc. **170**:348 (Sept.) 1925; The Therapeutic Value of Nonsurgical Drainage of the Biliary Tract, J. A. M. A.

majority of observers throughout the world who have carefully studied the method and have used it intelligently. Their corroborative clinical evidence of its usefulness is overwhelming and is well known to the students of this subject. The critics of the method, for the most part, have followed a modified technic of their own, usually cutting short the procedure in one way or another. They have thus deprived themselves of much of the diagnostic evidence that is really available and have consequently made various erroneous interpretations. Most of these errors have been pointed out in a previous publication.[3] On the other hand, some of the overly fulsome praise published by well meaning proponents has really been harmful to this useful procedure. Furthermore, we have learned that duodenobiliary drainage has been exploited by physicians poorly trained in the practice of general medicine and in special technic who improperly select for such treatment patients who manifestly require operation; by the type of trained nurse who advertises her proficiency in other technical procedures such as colonic irrigations; and by the out and out charlatan who trades on the psychic effect of removing a small amount of bile or bile stained fluid from gullible but purse-fat people whose interest is aroused by the pseudoscientific patter of such menaces to human health. It is deplorable that such practices exist. It furnishes entirely proper ammunition for some opponents of this method of treatment, a certain number of them overbalanced institutions with surgical axes to grind, but in turn it reflects discredit on them as well as on a method the merits and limitations of which are becoming more generally appreciated.

SURGICAL EVIDENCE

The surgical attempts in furnishing this proof have usually been failures. Within our knowledge, only three surgeons have gone on record as having seen the gallbladder empty in response to intraduodenal stimulation. The failure to observe contraction, vermiform movement or collapse of the gallbladder more frequently has probably been due to the effects of anesthesia, operative injury or shock or handling of viscera. A review of the adverse reports, however, will show that almost without exception the dark colored bile was recovered through the duodenal tube when the operator manually emptied the gallbladder. Some form of

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85:1541 (Nov. 14) 1925. Lyon, B. B. V.: The Evolution of Early to Late Gall Tract Disease, Memphis M. J. **3**:67 (March) 1926; Quelques considérations sur l'évolution, le diagnostic et le traitement—des affections du tractus biliaire, Presse méd. **34**:1361 (Oct.) 1926; The Nature, Diagnosis and Treatment of Cholecystitis, M. J. & Rec. **126**:620 (Nov. 16) 1927; 660 (Dec. 7) 1927; Duodenal Tube and Its Practical Value, Lancet **2**:918 (Oct. 29) 1927. Lyon, B. B. V., and Swalm, W. A.: Obstruction of the Cystic Duct of a Catarrhal Variety, J. A. M. A. **90**:833 (March 17) 1928.

3. Lyon et al (footnote 2, eighth reference).

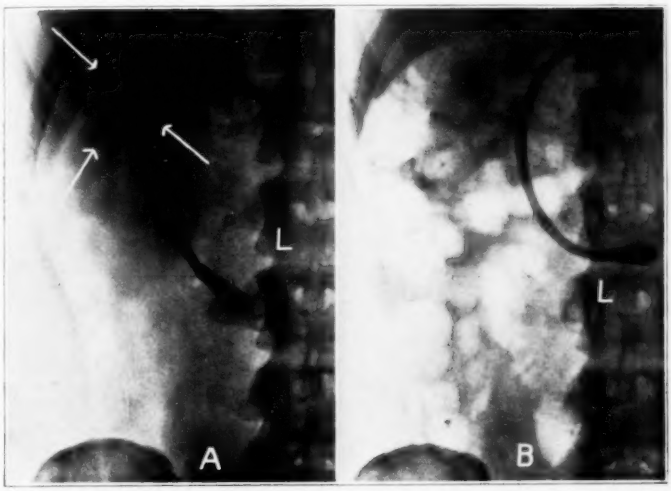

Fig. 1 (case 95134).—*A*, twelve hour film, showing shadow of gallbladder before drainage. *B*, sixteen hour film, three and a half hours after stimulation with 33.3 per cent magnesium sulphate solution; 140 cc. of brownish-black bile, rich in iodine was recovered, associated with disappearance of the shadow.

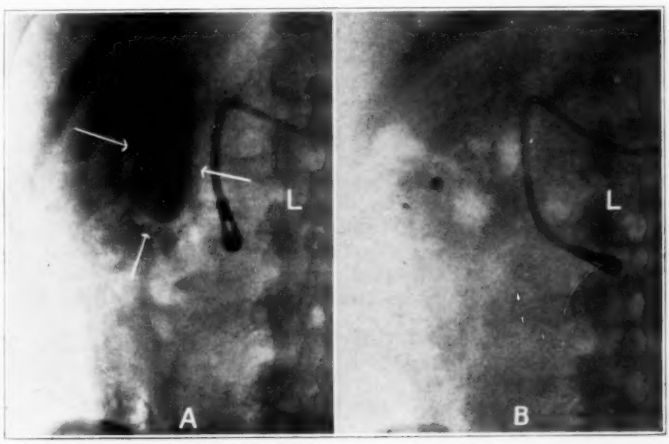

Fig. 2 (case 95136).—*A*, twelve hour film, showing shadow of gallbladder before drainage. *B*, sixteen hour film, three and a half hours after fractional stimulation with 33.3 per cent magnesium sulphate solution; 192 cc. of dark brown bile, rich in iodine, was recovered, with disappearance of the shadow.

obstruction of the cystic duct could account for the exceptions. It might be a matter of interest to have the observations of these three men put on record in this report.

In 1921, Prof. Adolph Sachs [4] of Nebraska reported the following cases, which have been abbreviated somewhat but without alteration of their context.

CASE 1.—Mrs. A. H., referred by Dr. G. Simanek, on medical drainage three days prior to operation showed "A" bile a light golden yellow; "B" bile a dark static bile; "C" bile a light lemon yellow. I was permitted to pass the duodenal tube in the above patient before she was anesthetized. The gallbladder was exposed and found to be fairly well distended, and before any exploration was made, 50 cc. of a 33.3 per cent solution of magnesium sulphate was introduced directly into the duodenum through the duodenal tube. In three minutes, bile started to flow. In five minutes, we started to get a real, dark golden bile (typical "B" bile) and the distended gallbladder gradually collapsed. I might compare this to the collapse of a balloon when the air is released (no contraction was observed). The gallbladder was then removed in the usual manner, and the bile in the collection bottle was apparently the same as that obtained from the removed gallbladder, only in greater dilution. I grant this was done under anesthesia and hence open to some objection; however, I offer it for what it is worth.

CASE 2.—Mrs. F. was referred by Dr. Simanek for medical drainage and treatment. On three successive medical drainages, only two types of bile were obtained, "A" and "C" bile. The case was referred back for operation as one not suitable for medical drainage. A diagnosis of stones, with probable obstruction of the cystic duct, was made. The duodenal tube was introduced before operation, as in the foregoing case. The usual gallbladder incision was made, the gallbladder exposed, and a small contracted gallbladder was seen. Fifty cubic centimeters of a 33.5 per cent solution of magnesium sulphate solution was introduced into the duodenum through the duodenal tube. No static bile appeared in five minutes, and the gallbladder remained unchanged. The gallbladder was then palpated and found to contain stones. It was removed and on opening it a stone was found, occluding the cystic duct.

CASE 3.—From the history and examination of Mrs. H., aged 35, a diagnosis of cholelithiasis was made. On several drainages, we found that at times "B" bile was present and at times not. The duodenal tube was passed as in the foregoing cases, and a moderate sized gallbladder was exposed. We stimulated with magnesium sulphate, and no change took place. On light palpation, a stone in the cystic duct was found. This was easily pushed back, and "B" bile appeared, which was apparently the same as that found in the removed gallbladder. There were several calculi present.

In 1923, Pribram [5] of Austria reported as follows:

Einhorn's duodenal tube was inserted before the operation; then a typical yellow-colored bile flowed out, and the abdomen was opened under ether narcosis. After the olive was ascertained to be in its proper position, 20 cc. of a 10 per cent Witte

4. Sachs, A.: Lyon-Meltzer Gall Bladder Drainage, Nebraska M. J. **6**:225 (Aug.) 1921.

5. Pribram, E. E.: Peptone Gallbladder Reflex, Klin. Wchnschr. **2**:1590, 1923.

peptone solution was introduced through the duodenal tube, and a dark, thick, oily bladder bile was recovered through the tube. The gallbladder contracted distinctly, and after several minutes a yellow liver bile again ran out.

In 1924, Matsuo [6] of Japan reported the two following cases:

CASE 1.—F. S., aged 37, according to the diagnosis made previous to operation, had a tumor in the left liver lobe. At operation, Oct. 27, 1923, a gallstone was found in the liver. As the disappointments resulting from operations performed by Lyon and others are explained by the fact that narcosis was induced, I wished to avoid this factor; not only was the patient not put under general narcosis, but also the pantopon-scopolamine solution was not injected. The abdomen of the patient was opened according to Kocher's technic under local anesthesia produced by procaine-epinephrine. By means of the usual incision, the gallbladder, which was as large as a good sized egg, was exposed; it was so greatly distended that the small blood vessels were scarcely visible.

Two hours before the operation, the duodenal tube was given to the patient, its proper location being determined by the roentgen rays.

The gallbladder was 7.5 cm. in length, measured from the point at which the gallbladder was attached to the inferior surface of the liver, and 4.5 cm. in breadth. During the operation, the duodenal content mixed with the typical bright yellow bile was flowing out. Then 40 cc. of a 33 per cent magnesium sulphate solution was introduced into the duodenum through the tube. Five minutes afterward, the typical brown bile, the so-called "B" bile, began to appear; the amount was 80 cc. Finally, after thirty-five minutes, the bright yellow bile ran out again.

At first the gallbladder was entirely filled, and it seemed so expanded that the blood vessels could not easily be seen. However, as the magnesium sulphate was given, and the dark, thick bile gradually dribbled out, the blood vessels became quite visible, standing out thickly; the gallbladder was no longer expanded, and, gradually decreasing in size, it was reduced at last to 4 cm. in length and 2.6 cm. in breadth. The so-called contraction was not observed, nor did the bladder collapse like a balloon from which the air was released, according to the description of Simanek. Rather, the size of the gallbladder decreased in an instant; estimated merely by the eye, the organ became one-fourth its previous size.

Forty cubic centimeters of a 1 per cent azorubin S. solution was then injected into the gallbladder, which almost resumed its original size. This procedure was painful to the patient. The organ, however, did not become nearly so large as before, being 5.5 cm. in length and 4.5 cm. in breadth. During this procedure, the bile from the duodenal tube had no trace of any red color. Forty cubic centimeters of a 33 per cent magnesium sulphate solution was then sent through the tube again, and this time it was observed that the gallbladder contracted very clearly and that almost all the dye solution was evacuated in a short time.

Judging from these results, I believe that, beyond any question, the bile flows out from the gallbladder into the duodenum by reason of the local application of magnesium sulphate.

CASE 2.—Z. O., aged 25, was operated on Feb. 14, 1924, for chronic appendicitis. Under the same conditions as those stated in case 1, observations were made with the assistance of Dr. Tsuji. Before the operation the olive was ascertained by

6. Matsuo, Iwao: Magnesium Sulphate as a Cause of the Evacuation of the Gall Bladder, J. A. M. A. **83**:1289 (Oct.) 1924.

means of the roentgen ray to be in its proper position; but from the time that the gallbladder was exposed, the bile ceased to flow out, and the instillation of magnesium sulphate solution did not bring about the appearance of the bile. Then it was found by palpation that the olive was far from the proper position required; that is, in the ascending part of the pars horizontalis inferior duodeni. When the olive was withdrawn to the proper position, near the papilla of Vater, the gallbladder was filled with 35 cc. of a 1 per cent azorubin S. solution, and the bile that ran out was not stained red. The instillation of 40 cc. of a 33 per cent magnesium sulphate solution was made, and two minutes afterward bile, colored deep red by dye, began to flow out; in the first five minutes, 45 cc. was recovered, and in the next five minutes 42 cc. The patient vomited a deep red bile. At this time, the gallbladder became small, although nothing like contraction could be observed to be taking place.

It is evident that the manner in which the gallbladder is observed to empty varies somewhat, although both Pribram and Matsuo definitely described it as a contraction. Yet, in these six cases, it appears that the gallbladder, unless too diseased or associated with obstruction of the cystic duct, will empty its liquid contents wholly or in part as a dark colored bile comparable to the "B" fraction.

EXPERIMENTAL EVIDENCE

I shall now consider contributions from the experimental laboratory. Investigations into the function of the gallbladder and especially in regard to its method of emptying have long engaged the interest of physiologists. Between 1893 and 1923 the hypotheses, based on experiments conducted, were greatly at variance, divergent results being obtained by various investigators, so that much confusion of ideas has existed. Since the various theories have been recently restudied carefully by Whitaker and by Higgins and Mann, they will not be reviewed here in detail. I shall place in evidence only the most authoritative opinions of the present day.

In 1923 and subsequently, Boyden [7] was first able to demonstrate that a meal rich in fats (egg yolk and cream) "induces the following cycle of changes in the gallbladder of the cat: (1) a period of slow emptying (two hours); (2) a collapsed or resting period marked by rearrangement of the mucosa (five hours) and (3) a period of rapid filling and bile concentration." Protein, such as egg white, and carbohydrate failed to provoke a similar response.

In 1926, Higgins and Mann [8] confirmed Boyden's results on certain fishes, amphibia, birds and mammals, finding that the gallbladder

7. Boyden, E. A.: Effect of Natural Foods on the Distention of the Gall Bladder with a Note on the Changing Pattern of the Mucosa Under Distention and Collapse, abstr., Anat. Rec. **24**:388, 1923; **30**:333, 1925; Anat. Rec. **33**:201, 1926.

8. Higgins, G. M., and Mann, F. C.: Observations on Emptying of the Gall Bladder, Am. J. Physiol. **78**:339 (Oct.) 1926.

emptied in response to a meal rich in fats in from one and one-half to three hours irrespective of whether the animal was carniverous or herbiverous in its normal habits. They then investigated the mechanism by which such emptying occurred in careful experiments on the garpike, guinea-pigs and dogs, and they concluded that: (1) the gallbladder empties through the cystic duct; (2) the gallbladder empties by contraction of its own intrinsic musculature; (3) secretory pressure is of little significance in emptying the vesicle; (4) intra-abdominal pressure is not a major factor in emptying the vesicle, and (5) the sphincter of the common duct is not a factor in emptying the vesicle, except that its relaxation permits the bile to pass to the duodenum under pressure incited by the contraction of the gallbladder.

In their studies on the exposed gallbladder after the meal rich in fats, these authors also found that there are localized areas of contraction, described as follows:

> The spherical bladder very gradually becomes somewhat hexagonal or pentagonal in outline, as its major axes reduce in dimension. Very frequently we have noted such extensive localized contractions as to induce the formation of numerous knob-like diverticula over the entire fundus of the vesicle x x x x. Under the experimental conditions the vesicle never entirely emptied its bile, as it had been observed to do in the killed animal.

In 1926, Whitaker,[9] after filling the gallbladder of dogs and cats with iodized oil and following its movement with the x-ray, came to the following conclusions: 1. The gallbladder is shown to empty its contents into the duodenum during the digestion of fats. 2. This emptying is produced principally by the muscular tunic of the gallbladder, extrinsic mechanical factors not having an appreciable effect. 3. Emptying probably does not depend on a reflex nervous mechanism involving extrinsic nerves since vagal stimulation has no effect, and denervated gallbladders empty normally. 4. There is no direct evidence that the expulsive action of the gallbladder is due to a hormone, although it invariably depends on the digestion and absorption of proteins or fats, especially the latter. 5. The action of the so-called sphincter papillae seems to be to allow the gallbladder to fill during the intervals between periods of digestion; but the vesicle will not empty after the sphincter is cut, feeding being necessary, as in normal animals, to effect this result.

It is of interest that Boyden and Whitaker found "that simply putting the cat under ether anesthesia, opening the abdominal cavity and

9. Whitaker, L. R.: Mechanism of the Gall Bladder, Am. J. Physiol. **78**:411 (Oct.) 1926; Experiences with Cholecystography, J. A. M. A. **86**:239 (Jan. 23) 1926; Mechanism of the Gallbladder and Its Relation to Cholelithiasis, ibid. **88**:1542 (May 14) 1927; Diagnosis of Gallbladder Disease, ibid. **88**:1791 (June 4) 1927.

quickly closing it will delay the gallbladder emptying for several hours. Deep ether anesthesia alone will prevent it. Even slight illness, such as wound infection may greatly inhibit emptying."

To the experienced observer of biliary drainage, deviation from the normal drainage response will often occur in sick patients who have diseased gallbladders, and not infrequently in sick or nervous patients with apparently normal gallbladders.

Hamrick's [10] conclusions from his experimental studies on the emptying of the gallbladder, which were reported in 1927, are closely in agreement with those of Whitaker and of Higgins and Mann.

The uniformity of agreement of these later investigators, when using similar methods of more modern development, should have considerable weight in explaining the divergent opinions of Doyon, Freese, Westphal, Bainbridge, Sweet, Halpert, Winkelstein, Diamond, Graham and other experimental workers with animals.

CHOLECYSTOGRAPHIC EVIDENCE

I shall now examine the evidence from various cholecystographic studies combined with duodenal intubation and biliary drainage.

In 1924, Silverman and Menville [11] were the first to demonstrate on human beings that the shadow of the dye-filled gallbladder could be substantially reduced in size and altered in shape following intraduodenal stimulation with magnesium sulphate. (The films of this study were exhibited at the meeting of the American Medical Association in 1924 and published in 1925.) The methods then used were less well established and the results less convincing than the films subsequently sent from various observers, notably Mariano Castex of Buenos Aires, Comstock of Saratoga, Lake of New York, Eberhard of Philadelphia and others. These films show clearly the marked reduction in size and shape of the dye-filled gallbladder that occurs after intraduodenal use of magnesium sulphate, which is promptly followed by the recovery of dark brown to black bile, usually within from ten to thirty minutes.

In 1926, Whitaker [12] confirmed the work of Silverman and Menville, although he, too, was unable to secure evidence of complete emptying of the gallbladder by such a procedure and stated that "we have found that almost invariably the decrease in size of the gallbladder shadow is greater if the patient has taken food especially fat, than after the

10. Hamrick, R. C.: Emptying of the Gall Bladder, Am. J. M. Sc. **174**:168 (Aug.) 1927.

11. Silverman, D. N., and Menville, L. J.: Observations of the Visualized Gall Bladder by Graham Method, with Reference to the Effect of Nonsurgical Biliary Drainage, J. A. M. A. **84**:416 (Feb. 7) 1925.

12. Whitaker (footnote 9, second reference).

intraduodenal injection of magnesium sulphate. This raises the question as to the value of nonsurgical biliary drainage by such means."

The improved results obtained in the present study equally raise the question as to the technic of intraduodenal drainage of the gallbladder which is employed.

The most recent utilization of this method of determining the source of the "B" bile has been undertaken by Lake,[13] who reported in December, 1927, the results of a study of eighteen patients. By means of magnesium sulphate either alone or followed by olive oil given intraduodenally, he recovered a good "B" bile fraction and caused marked reduction in the size of the shadow in five of eight cases, slight reduction in two and total disappearance of the shadow in one. In the latter instance, magnesium sulphate alone was used. To make a further check on the source of "B" bile, Lake had the various fractions of bile quantitatively tested for iodine (following the use of tetraiodophenolphthalein), and in this group found the "B" fractions to contain 10.8 times as much iodine as the "C" fractions and forty-eight times as much as the "A" fractions. In four of five cases in which small or doubtful "B" fractions were recovered only a slight reduction of shadow was obtained, and in one no reduction. In this group the "B" bile contained less iodine and the "C" more than in group 1. In five patients who failed to deliver "B" bile, two did not show a gallbladder shadow; one showed a mottled shadow, one a semilunar shaped shadow and one an apparently normal shadow. "In no case did the shadow decrease in size following the drainage. The iodin content of these biles was about the same before and after the stimulation, only traces being found or none at all."

Lake summarized his study as follows:

1. The recovery through a duodenal tube of 1 ounce or more of brownish, dark greenish or black bile following the instillation of magnesium sulphate or olive oil is accompanied by a considerable decrease in the size of the gallbladder shadow by the roentgen ray, or (in one case) its disappearance.

2. The dark bile so obtained contains an average of 43 times as much iodine as the bile that precedes it and 10.8 times as much as the bile that follows it, and may be the only fraction containing any iodine (fourteen hours after the oral administration of sodium tetraiodophenolphthalein).

3. When no dark bile is recovered, even though large amounts of yellow bile appears, the gallbladder shadow is either absent or does not decrease in size.

4. When a smaller amount of dark bile or a larger amount of amber-colored bile is secured, the gallbladder shadow decreased slightly in size or (in one case) not at all.

Conclusion: The above results seem to indicate that samples of bile from the gallbladder can be recovered through the duodenal tube for microscopic and bacteriologic examination.

13. Lake, M.: Observations on the Origin of the "B" Bile Obtained by Lyon's Method of Biliary Drainage, Am. J. M. Sc. **174**:786 (Dec.) 1927.

It will be seen, therefore, that there already exists a large amount of evidence indicating that, with rare exceptions which can usually be accounted for, the gallbladder is the source of the dark colored bile ("B" fraction) recovered after intraduodenal stimulation with magnesium sulphate, peptone or olive oil. Oleic acid, as recommended by McClure and others, is also a good intraduodenal stimulant for evacuation of the gallbladder.

Ivy and Oldburg [14] recently announced that the duodenal mucosa contains a secretin which can be isolated and when injected intravenously will provoke evacuation of the gallbladder. In this connection it might be worth while to state that a French preparation of secretin prepared by Les Etablissements BYLA for Professor Chiray of Paris for stimulating the flow of external pancreatic secretion was obtained by us on a recent visit to Paris. Following the publication of Ivy and Oldburg, we tried out this French preparation using 3 cg. intravenously before any other stimulants were given on patients undergoing biliary drainage. Thus far, in eighteen tests on sixteen patients there has been recovered only a trace of "B" bile in four and none whatever in fourteen within from forty-five to sixty minutes after the injection of secretin, although good specimens of "B" bile were subsequently recovered within from two to thirty minutes after stimulation with magnesium sulphate in fifteen of the eighteen tests. It may be that Ivy's secretin contains a specific gallbladder "principle" which is absent in the French preparation.[15]

Various men have sought to show that the source of the "B" bile is not necessarily the gallbladder. The case reported by Dunn and Connell [16] in 1921, suggesting a possible extra vesicle source for "B" bile, was for a time the most difficult one to interpret correctly.

In 1922, we [3] pointed out that it might be possible to recover a dark colored bile from a cholecystectomized patient with a dilated extra hepatic or intrahepatic duct system, or in hepatic cirrhosis associated with long continued biliary obstruction, and we suggested that this might be the explanation of the recovery of such static bile as was reported by Dunn and Connell in their patient who had had fifteen operations on the biliary tract.

It was not until 1926 that rather conclusive proof of this assumption was furnished by Counseller and McIndoe,[17] who showed the dilatation

14. Ivy, A. C., and Oldberg, E.: Contraction and Evacuation of the Gall Bladder by a Purified "Secretin" Preparation, J. A. M. A. **90**:445 (Feb. 11) 1928.

15. This study will be reported more fully elsewhere.

16. Dunn, A. N., and Connell, K.: Report of a Case of Hepatoduodenostomy with Some Observations on the Lyon-Meltzer Method of Biliary Drainage, J. A. M. A. **77**:1093 (Oct. 1) 1921.

17. Counseller, V. S., and McIndoe, A. N.: Dilatation of the Bile Ducts (Hydrohepatosis), Surg. Gynec. Obst. **43**:729 (Dec.) 1926.

of the biliary tree which takes place in chronic partial or complete obstruction of the extrahepatic duct system or in chronic calculous cholecystitis. We believe that those experienced in biliary drainage will agree that patients so studied after cholecystectomy will usually fail to deliver a "B" fraction; and that in the occasional exceptions a review of the case will indicate the likelihood of dilated ducts with sacculi or intrahepatic stasis. Such patients usually are jaundiced, have chronic disease of the liver or have had several operations on the upper part of the abdomen. With this review of previous evidence bearing on the subject, I shall report the results of the present study.

REPORT OF PRESENT STUDY

Four of nineteen cases were discarded from analysis because of failure to intubate the duodenum for reasons which will be discussed later. The remainder (fifteen cases) have been divided into two groups, the first of which requires little if any discussion. In six patients (numbers 95096, 95105, 95134, 95136, 95137 and 95171) of group 1 (table 1) in whom after oral administration of the dye excellent gallbladder shadows appeared and in whom good "B" fractions rich in iodine were recovered, the shadow was made completely to disappear after biliary drainage, as shown in the accompanying illustrations. Four of these patients had three fractional magnesium sulphate stimulations, one had one magnesium sulphate stimulation, which recovered 70 per cent of the "B" fraction, followed by olive oil, which recovered the remaining 30 per cent, and one had one peptone stimulation alone.

The duration of drainage averaged three hours and ten minutes, although in most cases all of the "B" bile was recovered within the first ninety minutes. It is worthy of comment that in all of these six patients the position of the duodenal tube as shown by the x-rays was favorable for good drainage; all of them had had a good night's sleep and none were nervous. Clinically, none showed advanced pathologic changes in the gallbladder, although all had symptoms, some physical manifestations and bile suggestive of those of early cholecystitis. The amount of "B" bile recovered ranged between 100 and 192 cc., averaging 142 cc.; the amount of "C" bile recovered ranged between 190 and 750 cc., averaging 428 cc. The amount of iodine in "B" biles ranged between 3.4 and 9.6 mg. per cubic centimeter of bile. The amount of iodine in "C" biles ranged between 0.42 and 3.2 mg. per cubic centimeter of bile. The "B" bile iodine, averaging 6.9 mg., was more than four times as strong as the "C" bile iodine, which averaged 1.6 mg. In this group are also included two patients, one of whom (95133) had had a poor night with diarrhea (four stools) and slight nausea. The tube was in poor position twelve hours after intubation but had reached a good position before the sixteen hour picture was

TABLE 1.—*Data in Group 1*

Case Number	Sex	Age	Reaction to Capsules	Position of Tube at		Density of Gallbladder Shadows				Reduction in Size of Shadow	Iodine, Mg. per Cc.		Cc. of Bile		Stimulation Used
				12 Hours	16 Hours	12 Hrs.	16 Hrs.	18 Hrs.	Meal		"B"	"C"	"B"	"C"	
95096	F	30	0	Good		4	0	..	0	Complete	4.2	2.5	120	210	$MgSO_4$
95105	M	54	0	Good		2	0	..	0	Complete	9.6	0.42	100	300	$MgSO_4$ and oil
95134	M	30	0	Good		4	1	0	0	Complete	6.4	3.2	140	500	$MgSO_4$
95136	M	35	0	Good		4	0	0	0	Complete	8.4	0.8	192	476	$MgSO_4$
95137	M	53	0	Good		4	0	0	0	Complete	3.4	1.3	125	400	Peptone
95171	M	28	0	Good		3	0	0	0	Complete	9.5	1.1	175	750	$MgSO_4$
95133	M	47	Nausea, diarrhea	Poor	Good	2	0	0	0	Complete	4.2	1.5	125	470	$MgSO_4$ and oil
95138	M	37	Diarrhea	Poor		4	1	..	2	¾	4.2	n.t.	125	190	Oil

TABLE 2.—*Data in Group 2*

Case Number	Sex	Age	Reaction to Capsules	Position of Tube at		Density of Gallbladder Shadows				Reduction in Size of Shadow		Iodine, Mg. per Cc.		Cc. of Bile		Stimulation Used
				12 Hours	16 Hours	12 Hrs.	16 Hrs.	18 Hrs.	Meal	B.D.*	M†	"B"	"C"	"B"	"C"	
95095	M	35	0	Poor	Good	0	0	..	0	.....		6.2	0.42	95	450	$MgSO_4$
95100	M	46	0	Good		3	0	..	0	Complete		10.5	0.4	145	375	$MgSO_4$
95135	M	49	Nausea, pylorospasm	Poor	Good	0	0	..	0	0	0	...	2.2	0	550	M-P-O‡
95102	M	52	Nausea, pylorospasm	Poor	Good	1	1	1	1	⅓	½	6.4	1.4	170	200	M-P-O
95175	F	55	0	Good		1	2	..	?	0	?	3.5	0.6	100	350	$MgSO_4$
95172	M	26	0	Good		3	4	3	4	⅓	C	3.6	1.3	205	250	$MgSO_4$
95170	M	44	Nausea, vomiting, diarrhea	Good		1	2	1	0	½	¾	19.6	3.2	100	400	M-P-O
										½	C	17.8	0.8	90	230	M-O§

* B.D. indicates reduction in size of shadow after biliary drainage.
† M. indicates reduction in size of shadow after meal rich in fats.
‡ M-P-O indicates $MgSO_4$-peptone-oil.
§ M-O indicates $MgSO_4$-oil.

taken. The iodine concentration of 4.2 mg. in "B" bile as compared to 1.5 in "C" bile suggested poor filling of the gallbladder. The dye shadow of grade 2 density disappeared after the drainage between the twelfth and eighteenth hour picture. Cholecystectomy and appendectomy were performed on this patient in December, 1927, and the following pathologic conditions were noted: chronic atrophic noncalculous cholecystitis and pericholecystitis; fibrous tissue in the liver, which was more distinct than usual; chronic adhesive appendicitis; a healed scar left by an ulcer on the duodenum, and mild colitis of the transverse colon.

In the second case (95138) a grade 4 shadow density was reduced to grade 1 after drainage in spite of the unsatisfactory position of the tube in a patient who was nervous after a poor night due to diarrhea. Here, too, the iodine content of 4.2 mg. in "B" bile was surprisingly low for a gallbladder that had apparently filled and concentrated well.[18] However, it must be noted that even after a meal rich in fats the gallbladder had not completely emptied.

In group 2 (table 2) are included seven patients, five of whom clinically showed a more advanced pathologic condition of the gallbladder and two of whom had had obstructive jaundice two months previous to this study. One of these (95100) failed to show a shadow of the gallbladder on the films made at the twelfth, sixteenth or eighteenth hour and likewise failed to deliver any "B" bile, although 550 cc. of "C" bile was obtained with an average iodine content of 2.2 mg. In addition this patient had nausea and pylorospasm with gross retention of food after twelve hours of fasting, and the duodenal tube was in a poor position. From the other recently jaundiced patient 170 cc. of "B" bile drained (after combined stimulation) which contained 6.4 mg. of iodine; the shadow of the gallbladder became distinctly smaller, although the degree of density did not change even after a meal rich in fats. The iodine of the "C" fraction, which amounted to only 200 cc. of bile, was 1.4 mg. Since Dr. Manges noted that the shadow of the liver was more dense, possibly poor elimination of the dye may account for poor density of the gallbladder. One hundred cubic centimeters of "B" bile of low iodine content (3.5 mg.) drained from a third patient (95102) after stimulation with magnesium sulphate, but failed materially to reduce the size of the gallbladder or its density of grade 1 until after the ingestion of a meal rich in fats; possibly the "B" bile with low iodine content represents thick "B" bile with poor iodine admixture. A fourth patient (95175) gave practically the same result. The next two patients are of interest. The first (95172) showed a good gallbladder shadow, which was reduced somewhat in size

18. In this patient the "C" bile was not tested.

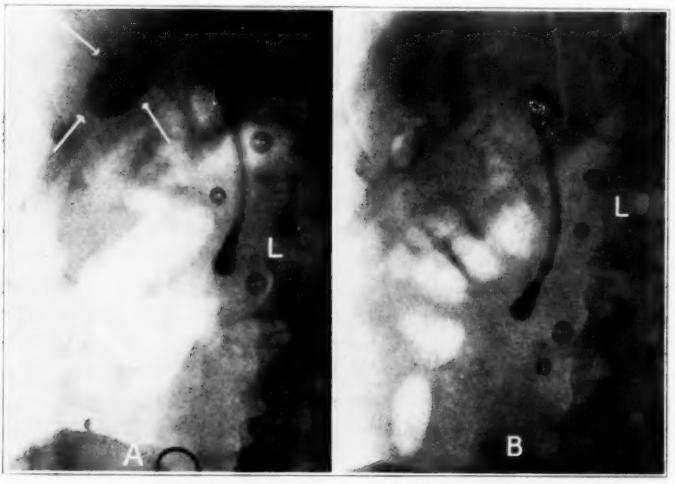

Fig. 3 (case 95137).—*A*, twelve hour film, showing shadow of gallbladder before drainage. *B*, sixteen hour film, three and a half hours after stimulation with 50 cc. of 10 per cent peptone; 125 cc. of blackish-brown bile was recovered. The shadow disappeared.

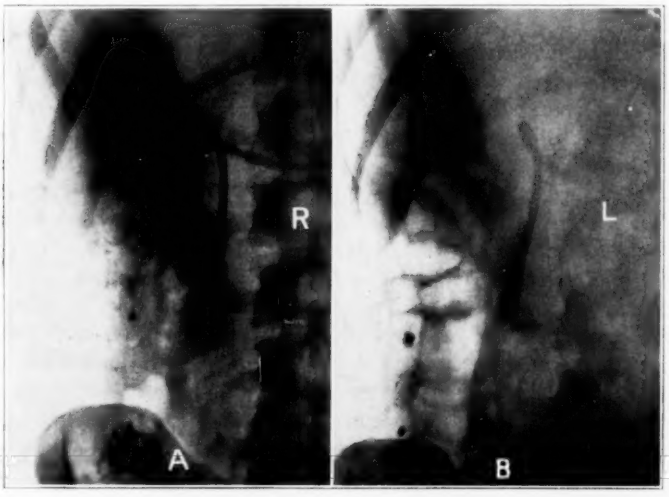

Fig. 4 (case 95171).—*A*, twelve hour film, showing shadow of gallbladder before drainage. *B*, eighteen hour film, about five and a half hours after fractional stimulation with 33.3 per cent magnesium sulphate solution; 175 cc. of greenish-black bile, rich in iodine, was recovered. The shadow disappeared.

but which failed to empty after either drainage or a meal high in fat content, although 100 cc. of normal "B" bile was obtained which contained the surprisingly high iodine content of 19.6 mg. The second patient (95170), who was nervous after a poor night due to nausea, vomiting and diarrhea, showed an unsatisfactory shadow not exceeding grade 1 density which diminished to one-half its size after eighteen hours and then emptied completely after a meal rich in fats. From this patient, after the administration of olive oil, we recovered 90 cc. of "B" bile with a high iodine content of 17.8 mg. The high iodine content of these two cases was a surprise and a matter of comment, so that the chemical determination was repeated, with exactly the same result. The interpretation of these cases is difficult, and they should be completely rechecked.

The remaining case in group 2 (95095) is also of interest. The gallbladder could not be visualized on films made at the twelfth, sixteenth or eighteenth hours. Nevertheless, after the administration of magnesium sulphate we secured 95 cc. of "B" bile with an iodine content of 6.2 mg. as compared to an iodine content of 0.42 mg. in 450 cc. of "C" bile. As this patient, whose condition was clinically estimated as early cholecystitis, had always given satisfactory "B" bile recoveries on previous drainages, we were at a loss to account for failure of gallbladder visualization; we repeated the study with Dr. Manges on Feb. 7, 1928, at which time a gallbladder shadow of grade 3 density at twelve hours disappeared at fifteen hours following which 145 cc. of "B" bile was recovered by drainage after stimulation with magnesium sulphate only. The iodine content in milligrams of this patient's bile fractions was as follows: duodenal fraction, 0.6; "B" bile after first stimulation with magnesium sulphate, 12.7; after second stimulation, 8.4; after third stimulation, 2.3; "C" fraction, 375 cc. after stimulation with olive oil; iodine content, 0.4. If this case should be accepted on the basis of recheck study, it would then properly belong to group 1.

In group 3 are placed the four patients (95106, 95107, 95173 and 95174) who were excluded from analysis because of the failure of duodenal intubation. The reasons for this failure are obvious. After the administration of the dye capsules all had poor nights with nausea, vomiting, diarrhea, excessive nervousness and pylorospasm. Three of these patients have definite clinical evidence of cholecystitis. In two of these (95107 and 95174), there was evidence of gross food retention in the contents of the stomach after twelve hours of fasting. One of these patients (95174) was continually nauseated throughout the preliminary gastric lavage and vomited the tube after the first film was made at the twelfth hour period, at which time a gallbladder shadow was not observed. The third patient (95107) showed a shadow of grade 1 density which failed to disappear although it was reduced to one-half its size after a meal rich in fats. In the fourth patient (95173), who

had pylorospasm and probably hyperperistaltic effort, when the tube was withdrawn it was found tied in a knot. In this patient the dye shadow of grade 3 density failed to disappear after a meal rich in fats, although it was reduced to one-fourth its original size.

COMMENT AND CONCLUSIONS

From the foregoing résumé it is evident, first, that the gallbladder empties its liquid contents largely by means of its intrinsic musculature and that such factors as diaphragmatic pressure, respiratory movements, changes in intra-abdominal pressure, changes in tonicity of the duodenal wall and of Oddi's sphincter, which thus contribute to a milking-like action on the common duct, all play a relatively unimportant rôle. Second, good specimens of gallbladder bile may be obtained by duodenal tube after intraduodenal stimulation with magnesium sulphate, peptone and olive oil and to a lesser degree by some other substances.[19] Third, specimens of gallbladder bile are therefore procurable for direct microscopic, chemical and bacteriologic study in the majority of patients with various grades of pathologic changes in the gallbladder except when the cystic duct is obstructed by impaction of a stone, stricture or adhesions. Catarrhal obstruction of the cystic duct furnishes one important differential exception.[20]

The following exceptions, not concerned with block of the cystic duct, which prevent recovery of gallbladder bile should also be borne in mind: (*a*) chronic contracted fibrotic gallbladders, usually containing calculi, with thickened walls and destroyed musculature; (*b*) gallbladder atony to which we have referred in various publications and which appears to be identical with the "gallbladder inertia" described by Chiray and his various associates in the French school. These are probably overstretched gallbladders, some of them with paper thin walls; (*c*) discoordinated nerve control to the gallbladder and Oddi's sphincter in various neurolabile subjects many of whom show other evidences of an unstable nervous system.

The last two groups make up those persons whom Smithies and his associates[21] have described as exhibiting "physiologic block" as con-

19. Kalk, H., and Schondube, W.: Motility of Biliary Passages; Pituitrin Test of Gall Bladder in Catarrhal Jaundice, München. med. Wchnschr. **73**:353, 1926. Chiray, M.; Lebon, J., and Galligari, H.: Action of Certain Stimulants of Vegetative and Endocrine Systems on Contraction of Gall Bladder in Man, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:103, 1926. Meyers, S. G.: Emptying of the Gall Bladder with Especial Reference to the Use of Pituitrin, Am. J. M. Sc. **175**:405 (March) 1928.

20. Lyon (footnote 2, nineteenth reference).

21. Smithies, F.; Karshner, C. F., and Oleson, R. B.: Nonsurgical Drainage of the Biliary Tract, J. A. M. A. **77**:2036 (Dec.) 1921.

trasted with "mechanical block." The condition in group A will at all times prevent recovery of gallbladder bile and will give strongly positive cystographic evidence of chronic surgical cholecystitis. The patients in groups B and C can usually be made to drain gallbladder bile subsequently: in group B, by exercise of the atonic musculature by a dietary rich in fats and by duodenal drainage frequently repeated; in group C, by bromides or other sedatives and antispasmodics such as atropine administered hypodermically or belladonna given by mouth until a physiologic effect is produced.

Since this study was designed to prove that the gallbladder can empty its liquid contents following intraduodenal stimulation and that such contents represent the source of the "B" bile, it would have been better if we had selected normal subjects with normal gallbladders. We believe it safe to assume that if we had done so, the results in our favor would have more nearly approached 100 per cent.

Nevertheless, our results clearly indicate that in patients with unobstructed cystic ducts and less advanced cholecystitis the gallbladder is the source of "B" bile and empties it after intraduodenal stimulation, as demonstrated by group 1; that in group 2, in patients with more advanced pathologic changes, the results, although less good, cannot be construed as vitiating the value of duodenal drainage but merely limit the scope of its therapeutic usefulness, as we have pointed out in earlier publications. We have learned by previous clinical experience that many patients representative of group 2 will give so much better results on repeated drainages as to justify, in properly selected cases, a continuance of nonsurgical management.

Finally, we hope that as a result of the evidence submitted, further controversy in regard to drainage of the gallbladder by the duodenal tube may be unnecessary.

We should now turn our attention to investigating the value of duodenal biliary drainage as an adjunct therapeutic agent in various problem diseases, such as hepatic inflammations, infections and cirrhoses; various hepatic splenopathies; pernicious anemia; diabetes; the medical variety of peptic ulcer; some forms of arthritis, asthma, and epileptoid seizures suspected of hepatic intestinal toxic or infectious origin, and various postoperative sequelae, such as residual cholangeitis, adynamic ileus and persistent singultus.

Some favorable reports of clinical improvement already exist, and by reason of new advances in physiology and biochemistry many avenues of investigation might be profitably followed.

GALLOP RHYTHM IN HYPERTENSION*

HERMAN MOND, M.D.
AND
ENID TRIBE OPPENHEIMER, B.Sc.
NEW YORK

Gallop rhythm has long attracted the interest of both the clinician and the physiologist. It has always been regarded as a warning of a serious condition of the patient, and even though the belief that it invariably indicates a fatal issue has had to be abandoned, its grave prognostic significance is still unquestioned. The theories to explain the mechanism have been numerous, and consequently the literature on the subject is prolific.

In this paper, we attempt to elucidate the dynamic factors connected with the production of this extra sound by means of graphic methods, giving exact records of the sounds and their relationship to the electrical and mechanical phenomena of the heart cycle.

We are concerned only with the study of patients presenting the classic syndrome of Potain: gallop rhythm in cases of hypertension with more or less marked cardiac insufficiency. This type of patient is frequently found in hospitals, and has been the subject of numerous investigations from many points of view. All varieties of methods, graphic and otherwise, have been essayed on these patients; the literature, however, contains but few actual sound curves, of which the remarkable records of Lewis are the outstanding examples. Most of the other writers on the subject are content with records of the apex beat.

METHOD

The point of chief importance seemed to be the exact location of the extra sound in the heart cycle. To determine this, we used simultaneous records of heart sounds and electrocardiograms and, whenever possible, recorded also the venous pulse, arterial pulse and apex beat. As many as possible of these records were made simultaneously on the same strip of film; but in any case, an electrocordiogram was included with each set of mechanical records to serve as a standard of measurement. Lead III of the electrocardiogram was generally used.

We had at our disposal only one string galvanometer, which was needed for the electrocardiogram. We were therefore unable to utilize Einthoven's electrical method of recording heart sounds, though it is probably the most satisfactory procedure, as regards both precision and appearance of the records. The only other method approaching the necessary high sensitivity is that of Frank, which we adopted in the form of Wiggers' modification,[1] with a few additional minor changes.

* Submitted for publication, Sept. 15, 1928.
* From the Cardiographic Laboratory of Mount Sinai Hospital.

1. Wiggers, C. J.: Am. J. M. Sc. **153**:666, 1917.

The recording tambour (Frank's capsule) consists of a small metal cup (diameter, 8 mm.; depth, 6 mm.) with a typical Frank's segment, the cord of which was 6 mm. long. As an oscillating membrane, we employ an extremely fine film of rubber. This is freshly prepared immediately before use from a rubber solution readily obtained commercially, and known as rubber cement.[2] The solution is rather viscid, and by means of a glass rod a fine film can easily be drawn over the opening of the tambour. The film adheres closely to the edge of the tambour and vibrates freely. A minute glass mirror, cut from a silvered cover-slip, is placed directly on the membrane near the straight segmental edge, any possible contact of the mirror with the edge of the tambour being carefully avoided, to ensure its free movement. The placing of the mirror is an important point in the technic; this position—near but not touching the edge—has given us the most satisfactory results. The extremely small size and negligible weight[3] of our mirrors make it unnecessary to place them overhanging the edge, as was originally recommended by Frank.

The method as a whole is satisfactory and has the advantages of extreme simplicity and trustworthiness, which by far outweigh its defects. The main drawback lies in the fact that the sensitivity of the rubber membrane varies with the viscosity of the solution used and with changes of the temperature and moisture of the air. On some days we found it extremely difficult to produce a satisfactory sound capsule, but usually the vibration frequency of the membrane was sufficiently high for a reliable sound record. As this study was not concerned with an analysis of the sound vibrations as such, but rather with the determination of the time of their occurrence, we did not have any difficulty in obtaining useful curves with the average capsule.

The tube leading from the tambour connects by means of a rubber tube (inner diameter, 6 mm.) to an ordinary open glass funnel (from 30 to 60 mm. in diameter), which is placed directly on the patient's chest in the region where the extra sound is best heard, usually near the apex. Equalization of pressure and elimination of the coarse mechanical movements of the wall of the chest are effected by means of an open side tube, connecting the system with the external atmosphere.

All the other mechanical records have been obtained with similar Frank tambours covered with a thin rubber dam, the mirror being placed as in the sound capsule. The side tube, of course, must remain closed for this type of record. The length and caliber of the rubber tubing leading to the different tambours should be uniform. As a source of light for all mechanical records, we used, following the example of Wiggers, a carbon arc lamp with a narrow slit, and a simple optical arrangement for focusing the oblong beam of light on our set of tambours. From each mirror, the recording light ray was reflected on the slit of the camera of the electrocardiograph. The whole system was so placed that the use of prisms was obviated. The half of the film on which the beams played was darkened by means of a shutter between the galvanometer and the camera.

Since all mechanical records were made simultaneously with an electrocardiogram, an extra time marker was unnecessary.

Owing to the difference, however slight, of the angle at which the various beams of light pass through the slit of the camera, simultaneous points on our curves are not necessarily in a straight line vertically one above another. Synchronous points, therefore, have always been carefully checked at each experiment by means of a vertically moving shutter, which instantaneously cuts off or admits

2. This was recommended to us by Prof. D. J. Edwards.
3. The average weight of our mirrors was about 0.0006 Gm.

the various light beams. Wherever simultaneous points on the various curves are not situated in a vertical line above the electrocardiogram, the deviation is carefully measured and indicated on the tracings.

TIME RELATIONSHIP OF THE EXTRA SOUND

By means of these records, then, one can ascertain the exact time relations of the extra sound to other events of the cardiac cycle, and can consider which of such events may have a causal connection with

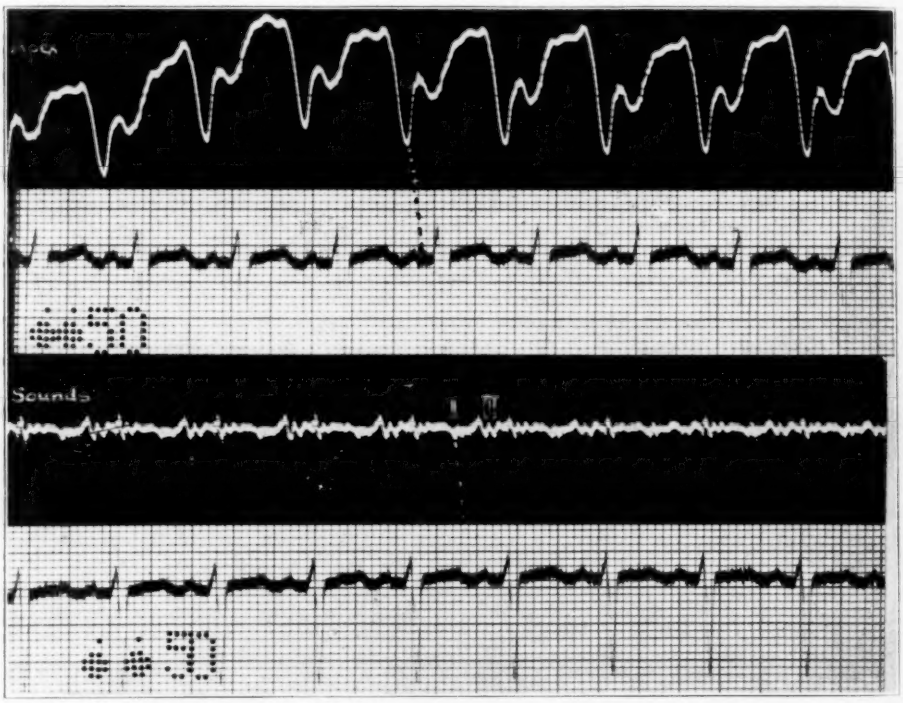

Fig. 1.—Electrocardiographic record of S. S., a man, aged 32, with hypertension and cardiac insufficiency and no murmurs, pulsus alternans and gallop rhythm. The average blood pressure was 200, systolic; 130, diastolic. Upper curve shows the apex beat, with large *a* wave and the lower, sounds. The extra sound is marked III.

the sound. In agreement with all previous observations, in true gallop rhythm the extra sound occurs during ventricular diastole, that is, between the second sound of one heart beat and the first sound of the succeeding cycle. The curves show that this extra sound on the phonocardiogram always occurs at the same time as the latter half of the P wave

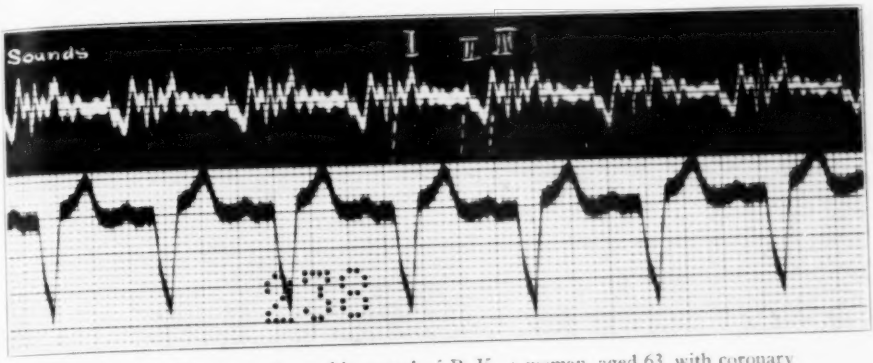

Fig. 2.—Electrocardiographic record of R. K., a woman, aged 63, with coronary disease, hypertension, intraventricular block and gallop rhythm. The average blood pressure was 170, systolic; 110, diastolic. The curves show the third sound simultaneous with auricular contraction.

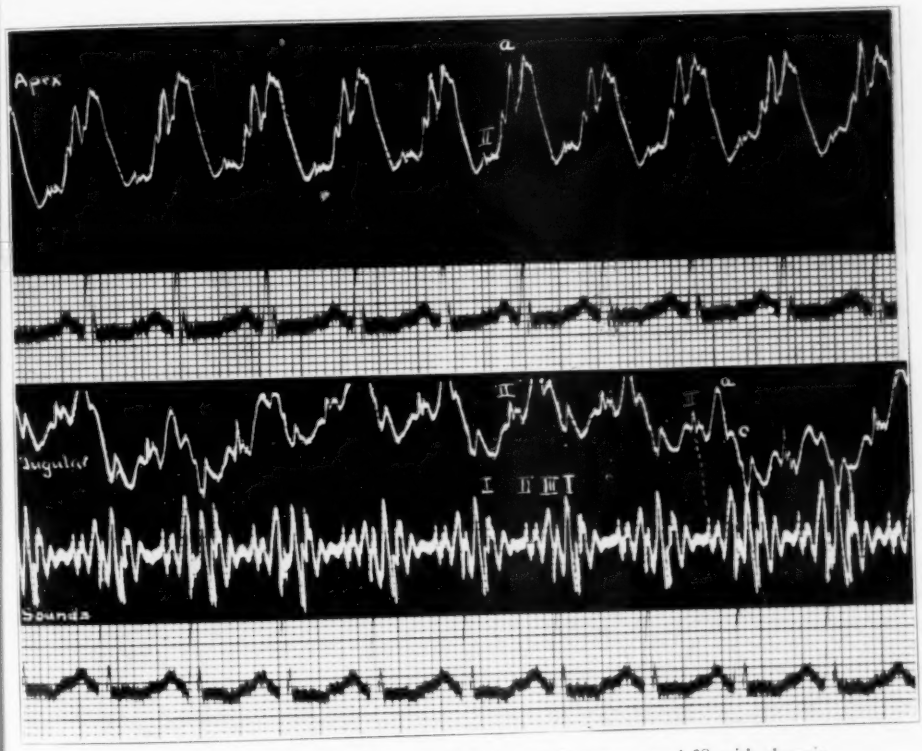

Fig. 3.—Electrocardiographic record of Samuel S., a man, aged 38, with chronic nephritis, hypertension, cardiac insufficiency, systolic murmur at the apex and gallop rhythm. The average blood pressure was 250, systolic; 160, diastolic. The upper curve shows the apex beat, with a prominent *a* wave and the lower, jugular pulse and sounds. A loud extra sound is marked III, and occurred simultaneously with auricular contraction.

of the electrocardiogram, and simultaneously with a large distinct wave of the apex beat and the *a* wave of the venous pulse (figs. 1, 2 and 3). This would therefore point to the auricular contraction as the determining factor, an idea which was first propounded by Charcelay,[4] in 1838, and which has been frequently reviewed by subsequent authors.[5]

The mere observation, however, of the apparent simultaneity of the auricular contraction and the gallop sound cannot be held as satisfactory evidence by itself of a connection between the two events. In many cases, a rather marked tachycardia is present, which apparently plays an important rôle in the dynamics of the phenomenon. Owing to the increased rate, the diastole is often so short that the extra sound vibrations are crowded in between the preceding second and the following

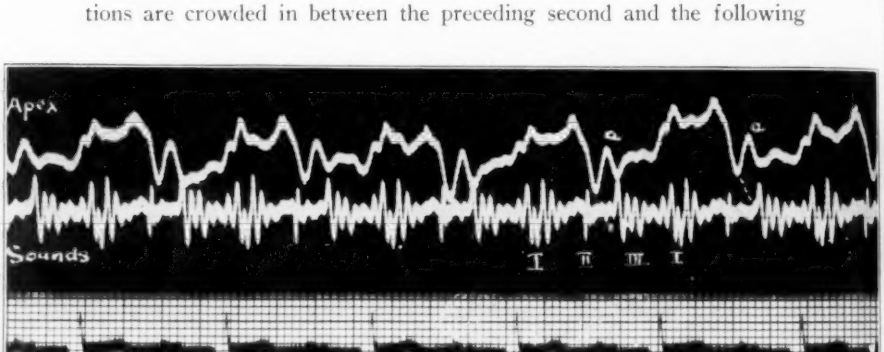

Fig. 4.—Electrocardiographic record of J. H., a man, aged 54, with hypertension, myocardial insufficiency, partial auriculoventricular block, aortic sclerosis and bronchopneumonia. The average blood pressure was 200, systolic; 130, diastolic. The extra sound (middle curve) starts 0.06 second after the peak of the P wave. The coarse and loud vibrations should be noted. In the apex beat (upper curve), the large *a* wave is simultaneous with the third sound. It should be noted how the broadening of the apex beat curve makes the *a* wave appear protodiastolic, while the extra sound is clearly middiastolic. Simultaneous points of apex and sound records are indicated by dotted lines.

first sound, thus occupying almost the whole of the period of ventricular diastole. It can be argued that because of the shortness of diastole almost any diastolic event must necessarily occur more or less

4. Charcelay: Arch. gén. de méd. **3**:393, 1838.

5. Krehl, L.: Arch. f. Physiol. (Du Bois-Reymond), 1889, p. 253. Lewis, Thomas: Lectures on the Heart, 1915, p. 66. Müller, Friedrich: München. med. Wchnschr. **53**:786, 1906. Robinson, Canby: Am. J. M. Sc. **135**:670, 1908.

simultaneously with auricular contraction. This difficulty, however, vanishes in cases showing partial auriculoventricular block, in which, because of a prolonged P-R interval, the groups of sound oscillations are separated from each other more definitely. One such case is shown in figure 4. The extra sound here forms a large group of vibrations, which are even more intense than those of the second sound, and are clearly related to the P wave in the electrocardiogram. This record, in conjunction with the previous observations, seems to us convincing proof that auricular contraction and gallop sound are indeed connected, since it is clear that shifting of the auricular contraction from its usual place in diastole is accompanied by shifting of the third sound. The measurement of the time relations shows that the extra sound in this case starts at an average time of 0.05 second after the onset of the P wave in the electrocardiogram, while the first sound has approximately

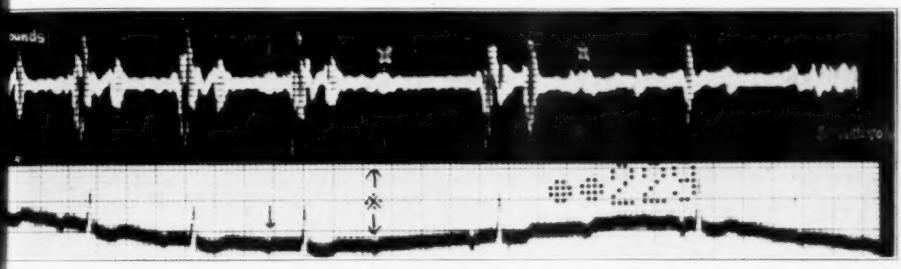

Fig. 5.—Electrocardiographic record of H. A., a man, aged 23, with mitral stenosis and insufficiency and presystolic and systolic murmur at the apex. It should be noted that the presystolic murmur shifts its place in diastole in the same sense as auricular contraction. When the auricular stimulus is blocked from reaching the ventricle (*) the murmur is recorded, isolated in early diastole.

the same time relation to the beginning of the Q.R.S. complex (0.06 second).

A similar situation may be found in so-called presystolic murmurs of mitral stenosis. Here, also, it is known that the murmur may change its position in diastole along with the auricular contraction. An interesting example of this behavior is given by a curve (fig. 5) taken of a patient with combined mitral and tricuspid lesions. The patient suffered from short attacks of paroxysmal disturbances of conduction. On the one record, the murmur may be seen to be presystolic, when auriculoventricular conduction is adequate; middiastolic, when the P-R interval is lengthened, and protodiastolic, when conduction fails, the ventricular complex is skipped and the P wave remains isolated during a long pause.

PROTODIASTOLIC AND PRESYSTOLIC GALLOP RHYTHM

As far as is shown by the records, it would appear that—at least in the hypertensive group of cases showing gallop rhythm—the distinction between protodiastolic and presystolic gallop is not of great significance.[6] Granting that in these cases gallop sound and auricular contraction are interrelated, it will depend entirely on the relative position of auricular contraction between the preceding second and the subsequent first sound whether the gallop is protodiastolic or presystolic. The factors determining this are, therefore, the rate of the heart beat, on the one hand, and the length of the auriculoventricular conduction interval, on the other.

1. *Rate.*—The shorter the diastole becomes with increasing rate, the nearer the extra sound approaches the preceding second sound. At a relatively slow rate, it is presystolic; at a higher rate, middiastolic, and it may even become protodiastolic, when with mounting tachycardia the interval between the end of the preceding systole and the next auricular contraction becomes shorter than the interval between the latter and the following first sound.

2. *Auriculoventricular Conduction Time.*—Just as changes of rate by mere shortening of diastole may diminish the interval between ventricular systole and the next auricular contraction, so may disturbances in conduction produce the same effect by lengthening the interval after which ventricular contraction follows auricular contraction. With increasing delay in conduction, the type of the gallop rhythm will again be changed from presystolic through middiastolic to protodiastolic. The case shown in figure 4 is of this type. That protodiastolic gallop may be due to prolongation of the auriculoventricular interval has already been suggested by Gallavardin,[7] on the basis of a similar case, in which, however, sound curves were not obtained. Here it may be remarked that although higher degrees of block are not common in gallop rhythm,[8] simple prolongations of the P-R interval are not infrequent; conduction time ranges generally about the upper limit of normal (0.2 second).

Quite aside from these considerations, it must be remembered that the clinical determination of the character of the gallop—whether protodiastolic or presystolic—becomes increasingly difficult with increasing rates. Even on the sound records it is sometimes hard to determine

6. Müller (footnote 5, third reference).

7. Gallavardin, L.: Arch. d. mal. du coeur **12**:410, 1920.

8. White, Paul D.: Clinical Significance of Gallop Rhythm, Arch. Int. Med. **41**:1 (Jan.) 1928.

(fig. 2); in fact, Potain himself, who originated the distinction, admitted that clinically it is often impossible to differentiate between the types.[9] The attempt at differentiation has nevertheless remained a favorite pastime in bedside medicine, in spite of its difficulty, perhaps because of it.

RECORDS OF THE APEX BEAT

A large diastolic wave in the records of the apex beat has been described frequently. Müller,[6] Canby Robinson[10] and others have assumed that in presystolic gallop this wave is an expression of auricular contraction. In fact, it has hitherto been almost the only graphic evidence of a connection between the accessory sound and auricular contraction. Our records of gallop rhythm (figs. 1, 3 and 4) demonstrate beyond doubt the simultaneity of this wave, the third sound and auricular contraction. The wave shows, moreover, the same variable

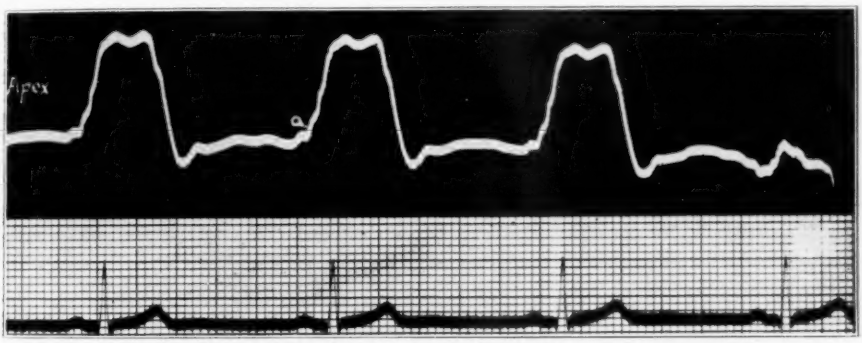

Fig. 6.—Electrocardiographic record of H. H., a man, with mitral insufficiency. Normal electrocardiogram. Normal apex beat, showing the small and insignificant normal *a* wave.

position in diastole as has already been demonstrated for the extra sound. The large size of this auricular wave in gallop rhythm is remarkable, and it was constantly observed in all our cases. It must be kept in mind that the *a* wave of the normal apex beat is small, often scarcely visible (fig. 6).

In connection with the use of the apex beat as a means of locating the auricular contraction, there is one source of error which has hitherto escaped attention. Owing to the slow rate at which relaxation proceeds in these cases, the pressure curve is markedly widened. Hence the *a* wave of the apex beat curve may follow the downstroke so quickly as to appear protodiastolic, even though it is actually middiastolic, as

9. Potain, C.: L'union médicale, 1875, vol. 20, p. 706.
10. Robinson (footnote 5, fourth reference).

shown by the sound record. Figure 4 is an interesting example of such a case. This contrast between apex beat and sound records as regards the apparent location of the extra sound in diastole becomes more important if one considers that the majority of authors have relied almost entirely on records of the apex beat.

ACCESSORY SOUNDS OF OTHER TYPES

The classic form of gallop rhythm, that observed in hypertensive disease, therefore, is characterized by a third sound occurring simultaneously with auricular contraction. As the term "gallop" has often been used rather loosely to describe almost any third sound appearing in diastole, it seems worth while to mention briefly certain types of extra

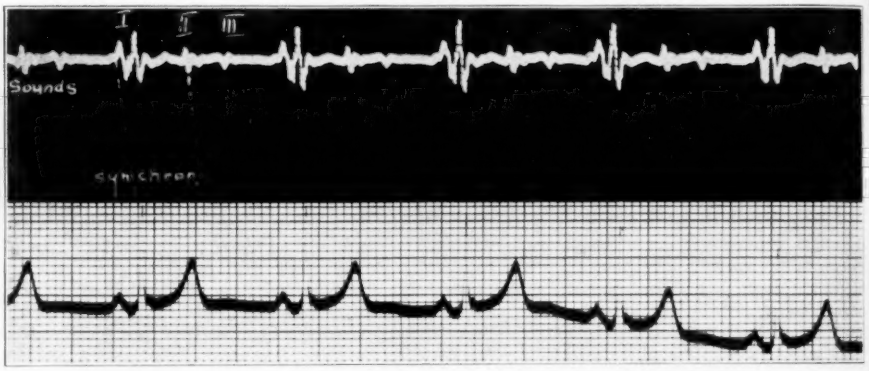

Fig. 7.—Electrocardiographic record of a man, aged 23, with systolic murmur at the apex but no diastolic murmur. The roentgenographic appearance of the heart, the blood pressure and the electrocardiogram were normal. The sound record shows a typical physiologic third heart sound.

sounds with a definite difference in mechanism. We distinguish two main groups:

1. The physiologic third heart sound has been described by many modern writers (Gibson,[11] Einthoven,[12] Thayer,[13] and Hirschfelder [14]), but satisfactory evidence as to its origin is not yet available. A glance at a record (fig. 7), however, convinces one that auricular contraction at least is not responsible for it; the mechanism is certainly not the

11. Gibson, A. J.: Lancet **2**:1380, 1907.
12. Einthoven, W.: Arch. f. d. ges. Physiol. **120**:31, 1907.
13. Thayer, W. S.: Boston M. & S. J. **158**:713, 1908.
14. Hirschfelder, A. D.: Diseases of the Heart and Aorta, Philadelphia, J. B. Lippincott Co., 1918, p. 173.

same as that of gallop rhythm in hypertension. According to Bridgeman,[15] the sound occurs generally 0.47 second after the onset of the anacrotic wave of the apex beat. The same author suggests vibrations of the auriculoventricular valves as a possible cause, while Einthoven [12] located the point of origin in the aorta or aortic valves. There is not, however, definite proof of either of these assumptions.

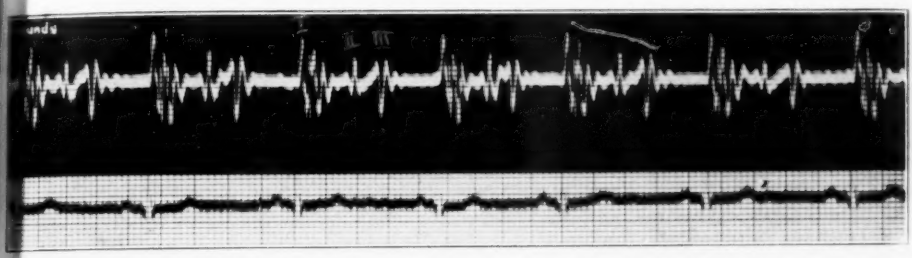

Fig. 8.—Electrocardiographic record of N. W., a boy, aged 16 years, with rheumatic fever, mitral insufficiency and stenosis. The blood pressure was 104, systolic; 60, diastolic. The group of oscillations marked III represent a "sound-like" diastolic murmur. At other periods, the patient showed an ordinary diastolic rumble.

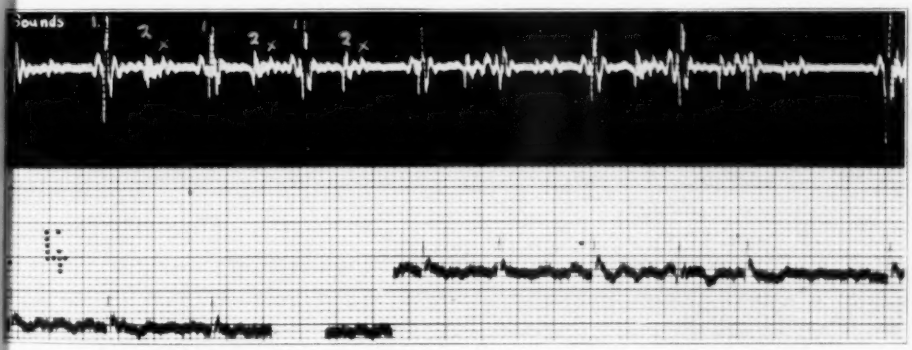

Fig. 9.—Electrocardiographic record of B. L., a woman, aged 39, with mitral stenosis and auricular fibrillation. The record shows reduplication of the second sound.

2. The so-called reduplication of the second sound in mitral stenosis (the claquement mitral of the French authors) is better known. It may be a rudimentary murmur or the initial phase of a diastolic murmur associated with the opening of the rigid mitral valves in early diastole (fig. 8). It is certainly independent of auricular contraction, since it often occurs in cases showing auricular fibrillation. Figure 9 shows

15. Bridgeman, E. W.: Heart **6**:41, 1915.

a reduplicated second sound in a patient with mitral stenosis with auricular fibrillation. On the other hand, we have never observed a typical gallop sound in hypertensive cases showing auricular fibrillation, which is in accordance with the observation of Lewis [16] that presystolic gallop disappears in auricular fibrillation.

Both of these types of accessory sounds are easily distinguished clinically from gallop rhythm. They both lack the peculiar tactile character of the gallop sound with its soft, diffuse shock, which often makes it felt rather than heard.[17]

MECHANISM OF GALLOP RHYTHM

In the group of cases investigated—all showing hypertensive cardiac insufficiency—we have satisfied ourselves that auricular contraction and the extra sound are simultaneous. While our records show this fact unequivocally, the view that an audible auricular contraction is responsible for gallop rhythm is by no means a new one. In fact, Charcelay,[4] the first observer who gave a lucid description of the phenomenon, advanced this theory as long ago as 1838, assuming that the contraction of a hypertrophied auricle might occasionally become audible. Although he did not use the expression "gallop," there is no doubt that this is what he was describing. We do not intend to attempt a complete survey of the immense volume of literature on gallop rhythm, more particularly as a review on the subject was published last year by Holt.[18] In passing we might mention that Charcelay's view found little acceptance in the subsequent decades and was in turn replaced by such theories as those of asynchronism,[19] polysystole,[20] active dilatation in diastole,[21] and contraction of papillary muscles.[22] Potain [9] was the first to distinguish between protodiastolic and presystolic gallop rhythm. According to him, the main factor is a rigid, fibrosed ventricle which must be forcibly distended by the inflowing blood. It is this sudden distention of the rigid muscular wall which, in his opinion, leads to the production of the third sound. In his theory, the rôle of the auricular contraction is neglected; whenever the blood flow suddenly distends the ventricle during diastole, the sound will occur. This, of course, fitted well into Potain's principle distinction between protodiastolic and presystolic gallop rhythm. More recently, the theory of auricular origin was again

16. Lewis (footnote 5, second reference).
17. Potain, C.: Semaine méd. **20**:175, 1900.
18. Holt, E.: Am. Heart J. **2**:453, 1927.
19. Bouveret, L., and Chabalier: Lyons méd. **60**:241, 1889.
20. D'Espine: Rév. de méd. **1**:117, 1882.
21. Brauer: Verhandl. d. Kong. f. inn. Med. **21**:189, 1904.
22. Chauveau, A.: Thèse de Paris, 1902, no. 315.

taken up by George Johnson [23] and later by Müller,[6] Canby Robinson [19] and Laubry and Pezzi.[24] All these authors, however, maintain the distinction between protodiastolic and presystolic gallop.

In our opinion, however, this distinction is of value only if two different types of mechanism are designated. As has been stated a mere variation in the length of diastole may so alter the relation of the third to the preceding second and the following first sound as to produce either of these types of gallop. The distinction apparently loses its significance if the same mechanism can in one instance produce protodiastolic, and in the next presystolic, gallop rhythm, just because the sinus rate happens to be different in the two cases. If, however, protodiastolic gallop should prove to be due to an essentially different mechanism, the distinction between this and presystolic gallop would be of great importance. According to Canby Robinson and others, protodiastolic gallop corresponds to an exaggerated "physiologic" third sound, while the typical presystolic gallop is due to an audible auricular contraction—two radically different mechanisms.

The physiologic third sound, whatever may be its origin, whether it is due to vibrations of the auriculoventricular valves in early diastole or to some other mechanism, is not due to an active contraction of any part of the heart. It is most frequently and almost exclusively found in young persons; it varies with the position of the patient, and it is rarely heard in the broad chested type of patient, who so often shows gallop rhythm. Occasionally the physiologic third sound is loud and exaggerated, but here the exaggeration has by no means the ominous significance of gallop rhythm.

The situation is entirely different with those hearts which exhibit audible auricular sounds. All our cases of gallop rhythm suggested this type of mechanism and, in contrast to the preceding group, presented definite evidence of heart failure.

The conditions under which auricular contractions become audible are apparently definitely abnormal. This leads to the questions:

1. Why is auricular contraction not heard under normal conditions?
2. What are the conditions that make auricular systole an audible event?

The fact that the normal auricular contraction is inaudible certainly needs explanation. That the mass of muscle is not too small to produce a sound is shown by Krehl's [25] observation that auricular sounds occasionally become audible in the heart of a dying dog; when heard, they are weaker than the ventricular sounds but are definitely perceptible.

23. Johnson, George: Lancet **1**:697, 1876.
24. Laubry and Pezzi: Bruit de Galop, Paris, 1927.
25. Krehl (footnote 5, first reference).

The idea that auricular and first ventricular sounds fuse into one under physiologic conditions is not tenable. The interval between the occurrence of the two sounds is undoubtedly long enough for the recognition of two distinct entities, since acoustic vibrations separated from each other by an interval of even so little as 0.01 second can be perceived as two distinguishable sounds. There seems to be no reason why auricular contraction should not normally be heard unless there are factors causing the sound vibrations to be damped. This, we believe, is what actually occurs. In 1911, von Wyss [26] and later Bridgeman,[27] by means of excellent curves, showed that phonocardiographic records of normal persons occasionally present a small group of vibrations occurring at an interval of 0.07 second before the first sound.[28] These vibrations are evidently highly damped, as shown by their small excursions, which diminish so rapidly that often only a single wave is seen. This marked damping apparently depresses the vibrations below the level of audibility. It is not difficult to see that the chief factor in the production of damping effects must be the ventricle. In the normal heart the ventricle is completely relaxed when auricular contraction occurs, its walls forming a soft, flexible mass which yields readily to the slightest pressure of the inflowing blood. In this phase auricle and ventricle form one large cavity, whereof the soft ventricular portion not only fails to participate in the vibrations of the auricle, but acts as a damper that silences whatever vibrations may have been started by the sudden contraction of the auricle muscle fibers. The amount of damping is clearly proportional to this yielding capacity of the normal ventricular muscle in diastole. With rising tension of the ventricular wall, the damping influence must be diminished and the chances of audibility improved. Bridgeman [27] has already suggested that a slightly higher ventricular tension in his cases might account for the occurrence of presystolic sound waves on the curves.

Here we find ourselves in the midst of the central problem already referred to: What are the circumstances in which auricular contraction becomes audible?

As long as the damping action of the ventricle is preserved, auricular contraction remains inaudible. If, however, the ventricle has lost its silencing power, the reason for this change can only be an alteration in the state of its wall. We must assume that the ventricular wall is

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26. Von Wyss: Deutsches Arch. f. klin. Med. **101**:1, 1911.

27. Bridgeman, E. W.: Notes on a Normal, Presystolic Sound, Arch. Int. Med. **14**:476 (Oct.) 1914.

28. Einthoven's paper on the physiologic third heart sound contains a sound record with characteristic presystolic vibrations (Arch. f. d. ges. Physiol. **120**:31, 1907, fig. 5, table 1). The oscillations are small and damped, and have the same relation to the following first sound as in Bridgeman's cases.

no longer in a state of complete relaxation in diastole, but now offers a marked resistance to the entrance of blood during auricular systole. The pressure wave produced by the contracting auricle meets with a ventricular wall which no longer yields passively to every impulse; the pressure is raised suddenly in the large common cavity comprising both auricle and ventricle, and the whole of its surrounding wall is thrown into transverse vibrations. These, transmitted to the wall of the chest, are heard as the familiar third sound of gallop rhythm. As has often been stated, it is best heard near the apex, which is that portion of the vibrating muscle mass closest to the wall of the chest. In this conception, the extra sound is a combined auricular and ventricular effect, and the participation of the ventricle explains why a sound, auricular in origin, should be so well perceived over the ventricle.

This explanation involves two assumptions; first, an altered condition of the ventricular muscle, and second, an increased pressure in the auricle. Is there any evidence, experimental or otherwise, that would support the hypothesis that these changes are likely to occur under conditions of hypertension with cardiac insufficiency?

At first it seems paradoxic to suppose that a failing heart, which is commonly associated with a "weak" musculature, should present a ventricle of which the fibers are at an augmented tension. However, the experimental work of Frank,[29] Patterson, Piper and Starling,[30] Straub[31] and others has taught us that under certain experimental conditions this is actually the case. The dynamics of the heart working under increased resistance were first studied by Frank. In his well known investigations on the heart of the frog, he showed that the diastolic tension of the heart muscle determines the efficiency of the contraction. Hence a rise of peripheral resistance, which would of itself diminish the output, causes an increased initial diastolic tension that, by producing a stronger contraction, enables the heart to maintain its stroke volume. This mechanism of compensation, however, works only within certain limits; if the peripheral resistance rises beyond a certain critical point, then a further increase of diastolic tension fails to evoke a stronger contraction; on the contrary, the efficiency of the contraction diminishes, the stroke volume falls and insufficiency sets in.

Starling and his collaborators and later Straub, working with Starling's heart-lung preparation, were able to show that essentially the same mechanism prevails in the mammalian heart. As an illustration,

29. Frank, O.: Ztschr. f. Biol. **32**:370, 1895.

30. Patterson, S. W.; Piper, H., and Starling, E. H.: J. Physiol. **48**:465, 1914.

31. Straub, H., in Bethe, A., et al.: Handbuch der Normalen und pathologischen Physiologie, Berlin, Julius Springer, 1928, vol. 7, p. 254.

we reproduce curves from Straub's work [31] (fig. 10) recording the pressures in the left ventricle (upper group) and the left auricle (lower group) during an experiment with increasing arterial load. Curves 1, 2 and 3 show the pressures while the heart action is still efficient. One can observe the gradually increasing diastolic tension accompanied by a corresponding rise of systolic pressure. The systolic pressure curve is little widened. With the onset of insufficiency, however (curve 4), the diastolic tension still continues to rise, but the systolic pressure falls, and the widening of the curve becomes marked. For our purposes, it is particularly interesting to note the behavior of the auricular pressure. At first, during the stage of compensation, the pressure level rises

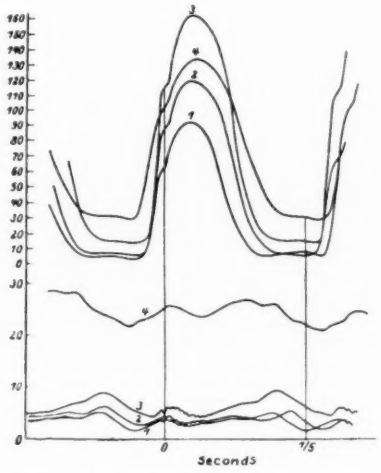

Fig. 10.—After Straub. The curves show the changes of intraventricular (upper series) and intra-auricular (lower series) pressure, during an experiment with increasing arterial load. The gradual increase of diastolic tension, particularly when the stage of insufficiency is reached (curve 4), should be noted. The intra-auricular pressure is likewise driven up at the same time.

but little and gradually, but as soon as the stage of insufficiency is reached (curve 4), the intra-auricular pressure rises abruptly to a considerable height.

One may therefore reasonably assume that the dynamics of cardiac insufficiency in human hypertension are basically of a similar nature. Both factors which we postulated for the production of gallop rhythm are at least made probable by the experimental work. The conception explains at once the prevalence of gallop rhythm in hypertensive cases with cardiac insufficiency, while the inconstancy of its occurrence follows from the functional nature of the phenomenon. It is often reported

that with recurring compensation the extra sound may disappear. Its production is the result of a functional process and does not depend, as in the original hypothesis of Potain, on a rigid fibrosis of the ventricle.

This conception of the mechanism of gallop rhythm supplies a natural explanation of other peculiarities connected with the phenomenon, particularly the constant finding of a large auricular wave in the apex beat, which is paralleled in the high auricular pressure in Straub's experiment.

The main condition, then, for the establishment of gallop rhythm is an increased diastolic tension of the ventricular muscle fiber, which may be present even before the appearance of the usual clinical signs of cardiac insufficiency. White [8] showed, however, that congestive heart failure was present in a majority of his cases, at least 61 per cent showing symptoms of cardiac insufficiency. White also made the observation that an

Fig. 11.—Electrocardiographic record of B. M., a woman, aged 53, with bronchial asthma, tuberculosis and hypertension. The record shows coarse vibrations corresponding only to those auricular contractions which are premature. The normal auricular contractions remain silent. The audibility of the auricular extrasystoles is perhaps favored by the patient's hypertension.

improvement in the clinical syndrome of heart failure under digitalis therapy was occasionally accompanied by the disappearance of the extra sound. This agrees with our own observation that gallop rhythm is not infrequently a temporary phenomenon, which is determined by the functional state of the muscle. Any cause, whether permanent or temporary, which changes the state of the ventricular muscle fibers to a heightened tension is likely to produce audible auricular sounds. A case in which auricular extrasystoles occur in early diastole might illustrate this fact (fig. 11). Here the extrasystoles frequently occur at an interval of about 0.06 second after the end of the second sound and therefore probably at a time when the ventricle is not yet fully relaxed. Consequently, the usual damping effect of the ventricle being eliminated, a group of vibrations appear in the sound curve simultane-

ously with the premature P wave of the electrocardiogram. This is the more interesting, since in the normal cycles of the same patient auricular contraction remains silent. We have already mentioned that tachycardia, with its shortened diastole, favors the production of gallop rhythm.

In this connection it may be recalled that auricular sounds are often heard in cases showing complete auriculoventricular heart block, in which the conditions for their audibility are particularly favorable. The loss of coordination between auricular and ventricular rhythms causes the auricle frequently to beat against a contracting, or only partially relaxed, ventricle, thus increasing the resistance to auricular contraction. This in turn tends to increase the force of auricular contraction. Other favorable factors are the frequently present hypertension, the large diastolic filling of the ventricle and its increased diastolic tension. Figure 12 illustrates such auricular sounds in complete heart block.

Fig. 12.—Electrocardiographic record of H. L., a man, aged 60, with complete auriculoventricular block, following rheumatic infection. An empyema complicating left-sided pneumonia necessitated the resection of a number of ribs; in this way a large portion of the heart was exposed, which remained merely covered with skin. The sound records are taken from the apex, and show the large, coarse vibrations accompanying auricular contraction.

It may be well to point out here that the auricular sounds in dissociation have exactly the same peculiar "palpable" quality as the extra sound in gallop rhythm. This curious tactile component of the gallop sound has been emphasized by many observers since its first classic presentation by Potain.[17] He described the accessory sound as dull and as "felt" rather than heard by the ear. This is the reason why it can be best perceived with the wooden stethoscope. The impulse can often be felt by hand on the precordium. This description of gallop sounds is exactly applicable to the case of auricular sounds in complete block, and this close resemblance is, in our opinion, an important additional argument in favor of the auricular origin of the accessory sound in gallop rhythm.

It is not necessary to look far for an explanation of the dull character of the sound. First, a valvular component does not enter into the

production of the "bruit de galop"; it is a pure muscular sound. Then, the cavity in which it originates is large, comprising both auricle and ventricle and thus tending to produce vibrations of a rather low frequency. Finally, the onrush of blood into the ventricle accelerated by the auricular contraction adds to the "palpable" character of the phenomenon.

SUMMARY

1. Gallop rhythm as seen in persons with hypertensive disease is produced by an extra sound simultaneous with auricular contraction.

2. Increased diastolic tension of the ventricle and increased intra-auricular pressure are regarded as the main factors in the causation of the accessory sound.

3. The relation of these conditions to the theory of cardiac insufficiency is discussed.

4. Protodiastolic and presystolic gallop rhythm, in the hypertensive type of case, are due to essentially the same mechanism.

5. The physiologic third sound and the reduplication of the second sound are distinguished from true gallop sound because they are produced by fundamentally different mechanisms.

EXPERIMENTAL HEART BLOCK *

CLAYTON J. LUNDY, M.D.
AND
LEWIS W. WOODRUFF, M.D.
CHICAGO

In the course of our experimental work on the heart, a new method was devised for increasing the intra-auricular and intraventricular pressures of the intact dog. This was done by tying a balloon on the tip of a properly bent glass rod (2 mm. in diameter) and inserting the rod into the right auricle or ventricle by way of the right jugular and innominate veins. This apparatus was connected with a mercury manometer and a pressure bottle which permitted raising the intra-auricular pressure to any desired amount. It was found unnecessary to use heparin to prevent coagulation, as clotting of blood was observed only once in twenty-five experiments. After a few trials, we were able to put the balloon into the right auricle, the right ventricle and the inferior or superior vena cavae at will. Control electrocardiograms were taken before and after tracheotomy, after tying the right jugular vein, after inserting the balloon and during the experiment after sectioning both vagi. Ether anesthesia was used.

RESULTS

With an intra-auricular pressure of from 15 to 60 mm. of mercury, there was gradual lengthening of the PR interval from 0.08 second to 0.2 second, a period of 2:1 block, establishment of an independent ventricular rhythm and finally complete suppression of the P wave.

After release of the pressure in the balloon, there was a gradual return to the control type of sinus rhythm with normal PR intervals.

This procedure was repeated three times with the same results in one dog, and similar observations were made on seven different dogs. These results were produced in one of three ways: (1) by mechanical pressure, (2) by anemia or (3) by a combination of mechanical pressure and anemia.

We were unable to obtain any similar results by placing the balloon entirely within the right ventricle or the inferior or superior vena cavae, nor could we obtain such results in experimental pericardial effusion, or in open chest operations in which the coronary sinus or the circumflex branch of the right coronary artery was tied. Double vagotomy did not have any effect on the results when done during the block produced with this method, nor did it prevent the appearance of the block.

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* Submitted for publication, Sept. 10, 1928.

* From the Department of Medicine of Rush Medical College University of Chicago.

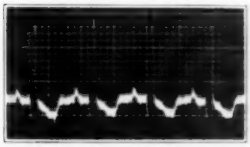

Chart 1.—Control after balloon was inserted into right auricle. PR :: 0.09 sec., PP :: 0.36 sec.

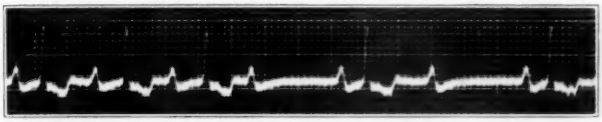

Chart 2.—Intra-auricular pressure increased, showing PR :: 0.21 sec., PP :: 0.51 sec.; two to one block.

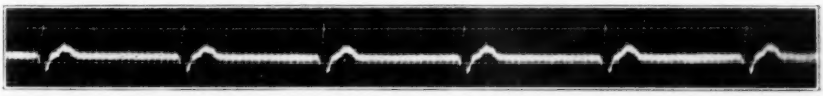

Chart 3.—Complete suppression of P wave with establishment of ventricular rhythm. RR :: 0.86 sec.

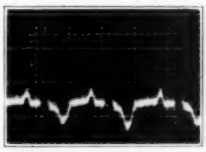

Chart 4.—Recovery after pressure in balloon was released. PR :: 0.10 sec., PP :: 0.40 sec. All tracings are of lead I; time markings at one twenty-fifth second intervals.

CONCLUSIONS

1. The PR interval was gradually prolonged into 2 : 1 and into complete block.

2. The rate of the sinus node was depressed.

3. Complete suppression of the sinus node was produced.

THE EXCURSION OF THE COSTAL MARGINS IN HEALTH AND IN DISEASE*

H. A. BRAY, M.D.
AND
J. L. WILSON, M.D.
RAY BROOK, N. Y.

Between 1913 and 1926, C. F. Hoover of Cleveland published a number of interesting articles on the mechanics of respiration in which he emphasized the diagnostic significance of the movements of the costal margins. According to this author, the intercostal muscles and the diaphragm have antagonistic actions. The intercostals enlarge the transverse and anteroposterior diameter of the lower part of the thorax in inspiration, and tend to draw the costal margins away from the median line and to widen the subcostal angle, while the contraction of the diaphragm increases the longitudinal diameter of the chest, and at the same time tends to draw the costal margins toward the median line, thus narrowing the angle between them. The extent and direction of the marginal motion are thus the result of the antagonistic forces exerted by the intercostal muscles and the diaphragm.

Hoover further claimed, however, that when the arch of the diaphragm is flattened from any cause, such as a pleural effusion, the muscle is placed at a mechanical advantage which gives it mastery over the intercostals as shown by the narrowing of the subcostal angle in inspiration; while if the convexity of the diaphragm is increased, as by a subphrenic abscess, the action of the muscle on the costal margin becomes less effective, the intercostals control the situation and the inspiratory effort causes flaring of the lower ribs with increase of the subcostal angle. To quote Hoover's words, " . . . there is exhibited in the costal border movements a very accurate index of the balance of power between diaphragm and intercostals." [1] Again, "The movement of the costal borders is a reliable index of the elevation or depression of the arch of the diaphragm." [2]

From all this it follows that careful observation of the marginal movements during inspiration will give valuable information about the condition of the diaphragm, and will enable the physician to draw important inferences therefrom. As Hoover said, "Such studies improve the accuracy with which one differentiates between infraphrenic and supra-

* Submitted for publication, Oct. 1, 1928.

* From the New York State Hospital for Incipient Pulmonary Tuberculosis.

1. Hoover, C. F.: The Importance of the Patient's Position in Studying Lung Excursion, J. A. M. A. **81**:1602 (Nov. 10) 1923.

2. Hoover, C. F.: The Functions of the Intercostal Muscles, J. A. M. A. **73**:17 (July 5) 1919.

phrenic disease and enables one . . . to differentiate between lesions which cause phrenic displacement and those which do not modify the plane of the diaphragm." [3]

In brief, Hoover thought that an inward movement of the costal margin during inspiration indicates either flattening or increased "activation" of the diaphragm, while an outward movement means that the surface of the diaphragm is convex, or that its activation is diminished relative to the intercostals. These modifications of the marginal motion constitute the so-called "Hoover's sign."

Considerable controversy has arisen regarding the validity of Hoover's conclusions and the importance of his "sign," and we were prompted to make a reappraisal of his views in so far as they apply to disease of the lungs and pleura.

We have been unable to establish any criteria of the degree of activation of the diaphragm aside from the amplitude of its excursion. Further, we have been unable to detect any such constant relationship between the position and contour of the diaphragm and the excursion of the costal margins as Hoover claimed.

Our observations lead us to the conclusion that the particular type of breathing (abdominal, lower thoracic, upper thoracic) and the lateral sway of the thorax, which often occurs during respiration, are more important in determining the direction of the costal excursion than are the position and contour of the diaphragm.

THE EXCURSION OF THE COSTAL MARGINS IN HEALTH

The movements of the costal margins were first studied in the healthy subject, and these observations were used as a basis to interpret their variations in disease. Seventy-one subjects were studied, forty males and thirty-one females, ranging between the ages of 18 and 40. Subjects presenting conditions which might modify the costal excursion, such as evident deformity of the chest, were excluded from the series. Observations were made during quiet, moderate and forcible breathing, in the standing, sitting and supine positions, and care was taken that the subject was relaxed at the time the observations were made.

In some healthy persons the thorax is slightly asymmetrical and the two sides of the chest expand unequally during inspiration. Of course, in these cases the costal margins reveal similar inequalities in their excursion since they are an integral part of the thorax and of necessity share in its movements.

Lateral flexion of the thorax during deep inspiration may cause marked inequality in the movement of the costal margins. The move-

3. Hoover, C. F.: Diagnostic Significance of Inspiratory Movements of the Costal Margins, Am. J. M. Sc. **159**:633 (May) 1920.

ment of the costal margin on the flexed side is limited or may even be inward, while there is a heaving motion of the opposite side, and its margin flares in an exaggerated manner.

Even without a change of posture, certain patients exhibit marked variations in the direction and extent of the marginal motions in the course of a single examination. Some persons have such control over the muscles of the thorax that they can vary the type of respiration and the extent and direction of their marginal motion almost at will. It is important to keep in mind these differences in the costal excursion in health, because they are readily confused with similar inequalities due to disease.

There is a definite relation between the excursion of the costal margins and the type of respiration. In order better to understand this relation, we instructed the subjects in this group to use the different types

Fig. 1.—*A*, healthy subject; abdominal inspiration. Respiration is conducted by the piston-like excursion of the diaphragm and the costal margins are practically stationary. *B*, lower thoracic inspiration. The thorax as a whole is not elevated and the costal margins move outward. *C*, upper thoracic inspiration. The thorax is elevated as a unit and the costal margins move upward and inward.

of breathing. It was noted that on purely abdominal inspiration (fig. 1, *A*) the costal margins are practically stationary. On abdominothoracic breathing, the outward excursion of the costal margins increases proportionately with the participation of the thoracic element, and is greatest when the respiration is purely thoracic.

The two types of thoracic respiration, lower and upper, influence the direction in which the costal margins move. On lower thoracic inspiration, the thorax as a whole is not elevated and the costal margins move outward (fig. 1, *B*); on upper thoracic inspiration the thorax is elevated as a unit by the accessory respiratory muscles of the neck, shoulder girdle and upper part of the thorax, and the costal margins move upward and inward (fig. 1, *C*). When the inspiration is partly upper and partly

lower thoracic, the inner portion of the costal margin may move inward, while the outer portion may move outward. In other words, with thoracic breathing, the extent of the excursion of the costal margins depends on the depth of the respiratory effort, but the direction of their movement is governed by the type of respiration. This holds true whether the person is sitting, standing or supine.

With the aid of the fluoroscope, tracings were made of the outline and position of the diaphragm on lower and on upper thoracic inspiration in the same subject at the same sitting (fig. 2). When compared, the tracings showed no significant differences, demonstrating thereby that the observed variations in the direction of the costal movements were not

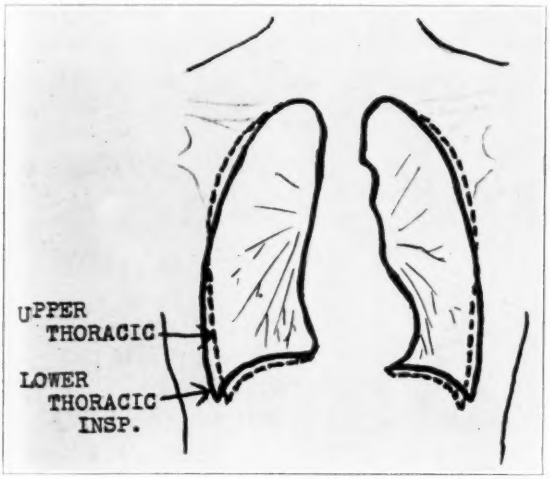

Fig. 2.—Composite diagram. The unbroken line represents the outline of the diaphragm on lower thoracic inspiration; the dotted line, on upper thoracic inspiration, as determined by fluoroscopic examination. The contour of the lines and their relative positions may vary somewhat in different persons but not markedly.

due to changes in the position and contour of the diaphragm. In brief, normal persons, by controlling the type of respiration, can reproduce at will the phenomena which, according to Hoover, should indicate definite pathologic conditions above or below the diaphragm.

EXCURSION OF THE COSTAL MARGINS IN DISEASE

With the foregoing observations in mind, we studied a group of diseases which either modify the excursion of the costal margin or effect changes in the position, contour and tonicity of the diaphragm. The

conditions studied comprised pleural effusions, pleuritic adhesions, pneumothorax, phrenicotomy, bronchial asthma, cardiac decompensation and ascites.

The same method of examination was adopted as in the healthy series, provided the condition of the patient permitted. In a few instances, only a single observation was made; in the others, the observations were repeatedly checked over a period of weeks or months.

Pleural Effusions.—The relation between the costal excursion and the depression of the diaphragm was studied in twenty-five patients with all degrees of effusion into the thorax, from small amounts to massive collections completely filling the affected side. The patients in most instances were kept under observation until the effusions had spontaneously absorbed, which permitted us to study the behavior of the costal margins with the diaphragm at widely different levels.

In twenty instances, including some of the larger effusions, no inward movement of the costal border on inspiration could be observed at any time. In the remaining five patients with massive effusions causing marked dyspnea, we detected an inward inspiratory movement of the costal border on the affected side. On inspiration, these patients flexed the thorax toward the diseased side to permit freer expansion of the healthy lung; when the dyspnea was relieved by the removal of a large amount of the fluid, the lateral flexion and the inward motion of the costal border promptly disappeared. This inward movement of the costal margin cannot reasonably be attributed to depression of the diaphragm, because, as previously noted, a similar movement of the margin occurs in healthy persons when the thorax is flexed.

It is conceded that a depression of the diaphragm by pleural effusion is often accompanied by modification of the costal excursion, but it is doubtful if the modification is caused by the alleged mastery gained by the flattened diaphragm over the antagonistic pull of the intercostal muscles. The wall of the chest is shoved outward to make room for the effusion just as the diaphragm is forced downward and the mediastinum is pushed inward. The costal border, being already held expanded by the fluid, is unable to respond in a normal manner to the outward impulse of inspiration and its movement is naturally modified.

Flattening of the Diaphragm Due to Costophrenic Adhesions.—In twenty-four cases we observed pleuritic adhesions between the diaphragm and the ribs, obliterating the costophrenic sinus (fig. 3, *A* and *B*). These localized adhesions caused various degrees of flattening of the diaphragm depending on their level. They diminished the diaphragmatic excursion, but so far as we could tell, did not interfere with its "activation." The lung above the flattened diaphragm was free from disease, or practically so in most of the cases, so that any

deviation of marginal motion could be attributed solely to change of contour of the diaphragm. This flattening of the diaphragm had no influence on the costal excursion on the affected side of the chest during quiet breathing. On deep breathing, no change was noted in approximately half of the cases; in the remaining cases, the flare of the affected costal margin was restrained to a greater or less extent. Yet in no instance did the costal margin move inward on inspiration except when there was a lateral sway of the thorax. In other words, the loss of convexity of the diaphragm, even to the point of flattening, failed to give the diaphragm mastery over the intercostals, as Hoover contended.

Pneumothorax.—The costal margins were studied in twenty-seven patients [4] in whom the affected lung had been partly or completely

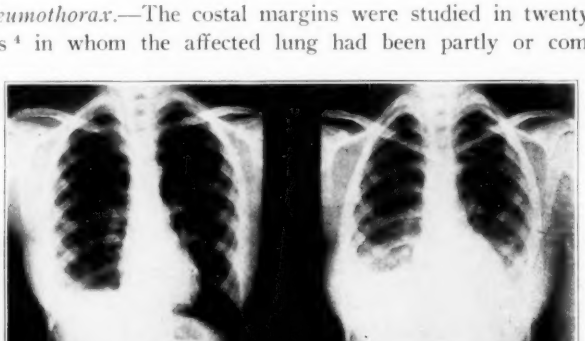

Fig. 3.—Comparison of the levels of the right and left diaphragmatic leaves on (*A*) deep and (*B*) quiet inspiration shows the right diaphragmatic leaf flattened and its motion greatly limited.

collapsed by artificial pneumothorax (fig. 4). In some, the diaphragm, as observed by the fluoroscope, retained its normal convexity; others showed every variation from this normal curve to absolute flattening and complete loss of its arch. In most instances, the motion of the affected side, including its costal margin, was restricted, while the direction of the movement conformed to that observed in the healthy subject. In the abdominal type of breathing, the costal margin did not move; in the lower costal type it moved outward; in the upper costal type of breathing it moved upward and inward. It was not observed that the presence or absence of diaphragmatic convexity influenced the direction of the marginal motion.

4. Many of these patients were seen through the courtesy of the staff of the United States Veterans' Hospital, Tupper Lake, N. Y.

Paralysis of One Leaf of the Diaphragm.—There were six patients observed in whom a phrenicotomy had been performed. On the side on which operation was performed, the diaphragm was paralyzed and assumed a position of extreme convexity in the thorax. According to Hoover, this should place the diaphragm at a great disadvantage, and the complete control of the intercostals should be reflected in a marked increase in the outward movement of the costal border on the affected side. Lemon [5] was unable to discover any change in the movements of the thorax in dogs after phrenic neurectomy. McKay [6] observed the excursion of the costal margin previous to and after phrenicotomy in twenty patients with pulmonary tuberculosis and did not note any change in its excursion following the operation. The cases observed by us like-

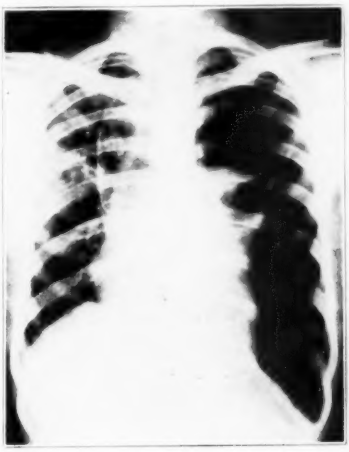

Fig. 4.—Artificial pneumothorax. The left diaphragmatic leaf is greatly depressed and flattened, yet the left costal margin moved normally outward on inspiration.

wise did not show any change in the movement of the costal margin following operation.

Asthma.—A series of observations was made on twelve patients suffering from periodic attacks of asthma. While they were free from spasm of the bronchi, their breathing was normal, of the lower costal type, and the excursion of the costal margin was outward. Tracings were made of the diaphragm during this time. When bronchial spasm

5. Lemon, Willis S.: The Physiologic Effect of Phrenic Neurectomy, Arch. Surg. **14**:345 (Jan.) 1927.

6. McKay, Raymond C., Cleveland City Hospital, Cleveland, personal communication to the authors.

recurred to a degree producing urgent dyspnea, the breathing was changed to the upper costal type and the costal margins moved upward and inward. Tracings were made of the position and movements of the diaphragm during this time, and were compared with those made while lower costal breathing was being carried on (fig. 5). The difference in the position or contour of the diaphragm in the two types of breathing was negligible and inconstant.

The study of the costal excursion and the position and contour of the diaphragm in asthmatic patients during and after an attack of bronchial spasm, demonstrates unmistakably that the direction of marginal motion is not due to an alteration in the contour of the diaphragm,

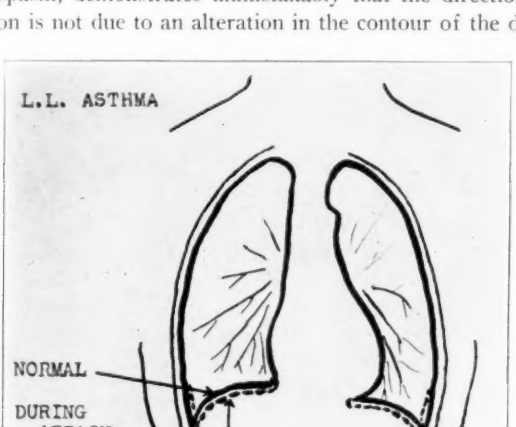

Fig. 5.—Asthma. The dotted line represents the position and contour of the diaphragm during an attack of bronchial spasm; the unbroken line, after the attack had subsided.

but to the change in the type of breathing necessitated by the respiratory demands.

Nonpulmonary Conditions.—We made observations in a number of patients with dyspnea resulting from cardiac decompensation. While the patient was free from dyspnea, lower costal breathing with the attendant outward movement of the costal margin was seen. When the dyspnea was urgent, the breathing changed, became upper costal in type, and the costal margins moved up and in. Fluoroscopic inspection of the diaphragm during both periods did not show any demonstrable change in its contour or position.

We observed the marginal motion in a few patients with extrathoracic disease with dyspnea, including ascites and uremia and found

that the extent and the direction of the costal movement is determined by the type of respiration at the moment of observation.

CONCLUSIONS

In our experience, the extent and direction of the excursion of the costal margin bear little if any relation to the position or contour of the diaphragm. The extent of the excursion of the costal margins depends on the depth of the respiratory effort, but the direction of their movement is governed by the type of respiration. Their movements may vary from time to time in the same patient, whether the disease is thoracic or extrathoracic, and can be reproduced at will by healthy subjects. We are forced to conclude that the modifications of the marginal motions which have come to be called "Hoover's sign" are not reliable guides to underlying pathologic conditions.

OCHRONOSIS

REPORT OF A CASE OF CARBOLOCHRONOSIS *

S. E. GOLDBERG, M.D.
DETROIT

Up to the present time there have been few reports in the English literature on the subject of ochronosis. The term ochronosis (Greek, pale yellow) was applied by Virchow,[1] in 1866, to the pigmentation of cartilages and cartilage-like tissues found at autopsy in a man, aged 67, who died of an aneurysm of the ascending aorta. Fine microscopic sections showed the pigment to be yellowish (ochre colored), but grossly the pigmentation was blackish. Indeed, the "rib cartilages, pelvic synchondrosis, and the intervertebral disks were so black that they appeared as if they had been dipped into ordinary ink." Since Virchow's time, fifty-one cases have been reported.

Albrecht[2] (1902) first suggested the relationship of ochronosis to alkaptonuria. Osler[3] (1904), however, was the first to recognize the condition clinically; he reported two cases of ochronosis with alkaptonuria which occurred in brothers. The clinical diagnosis was made because of the deep pigmentation of the cartilages of the ears and of the sclerotics in both and, in addition, in one of the brothers, of a remarkable ebony black discoloration of the skin of the nose and the cheeks.

In 1906, Pick[4] in Germany and Pope[5] in England each described a case of ochronosis which in each instance occurred in a patient who had applied wet dressings containing small amounts of carbolic acid to chronic ulcers of the leg continually over a period of many years. The pathogenesis of this disease was not discussed by Pope but was first pointed out by Pick, who recognized an exogenous form of ochronosis due to the introduction of phenol into the body, and an endogenous form occurring in patients with alkaptonuria. Pick also showed the pigment

* Submitted for publication, Sept. 27, 1928.

* From the Department of Pathology of the Krankenhaus-im-Friedrichshain, Berlin, Prof. Ludwig Pick, Director.

1. Virchow, R.: Ein Fall von allgemeiner Ochronose der Knorpel und knorpelaehnlichen Teile, Virchows Arch. f. path. Anat. **37**:212, 1866.

2. Albrecht, H.: Ueber Ochronose, Ztschr. f. Heilk. **23**:366, 1902; Zdarek, E.: Ueber den chemischen Befund bei Ochronose der Knorpel, ibid. **23**:379, 1902.

3. Osler, W.: Ochronosis: The Pigmentation of Cartilages, Sclerotics, and Skin in Alkaptonuria, Lancet **1**:10, 1904.

4. Pick, L.: Ueber die Ochronose, Berl. klin. Wchnschr., April and May, 1906, vols. 16 to 19 incl.

5. Pope, F. M.: A Case of Ochronosis, Lancet **1**:24, 1906.

to be closely related to melanin, although it differed from melanin in its chemical properties in a few minor details. In alkaptonuric ochronosis, the pigment results from the hydroxylated substances of the aromatic series (tyrosine and phenylalanine) under the influence of oxydative ferments (tyrosinase); in carbolochronosis, the pigment results from the hydroxylated benzol derivatives, hydrochinon and pyrocatechin. In alkaptonuria, there is a checking of the normal protein metabolism at an intermediate stage. Unlike the normal person, the alkaptonuric patient cannot burn the homogentisic acid (alkapton body) formed out of tyrosine and phenylalanine and therefore partly secretes it as such in the urine and partly stores it in certain of the body tissues in which it gives rise to the ochronotic pigment. In exogenous ochronosis, the pigment is the same, though it arises from hydrochinon.

In addition to the occurrence of the ochronotic pigment primarily in the cartilages and the cartilaginous tissues, Pick showed that the pigment might be deposited diffusely in the loose connective tissues, e.g., in the adventitia of the blood vessels, in the corium of the skin and in the smooth and striated muscles, as well as in the epithelial parenchyma of the kidney. He also raised the question of a third form of ochronosis, that associated with melanuria. Oppenheimer and Kline[6] reported a case which they believed falls into this category. This group is not sharply set off and probably includes a number of instances of alkaptonuric ochronosis.

The total of fifty-one cases may then be divided into three groups: the endogenous form which is congenital, the exogenous form due to the introduction of phenol into the body and the melanotic form of unknown origin. In every case of carbolochronosis recognized up to the present time, there has been a history of long continued application of phenol as an antiseptic dressing to ulcers on the leg. Since phenol is used in various ways in industry, it would be theoretically possible also to have carbolochronosis result from industrial poisoning, although good protective methods could probably guard against such an occurrence. As the era of the popular use of carbolic acid as an antiseptic is past, carbolochronosis may be said to be a dying disease. I am therefore reporting another case in which autopsy was performed and which has been studied especially from the point of view of the cartilaginous changes. Ella H. Fishberg,[7] who carefully treated the subject of carbolochronosis in 1924, collected reports of eleven cases in the world's literature. The following case will be the twelfth. In eight of these twelve cases, postmortem examinations were made, in four of the eight by Professor Pick.

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6. Oppenheimer, B. S., and Kline, B. S.: Ochronosis, Arch. Int. Med. **29**:732 (June) 1922.

7. Fishberg, Ella H.: Ueber die Carbolochronose, Virchows Arch. f. path. Anat. **251**:376, 1924.

REPORT OF CASE

History.—M. M., a woman, aged 63, unmarried, formerly a cook, was admitted to the Hufeland Hospital (Dr. Winter, director) on Aug. 28, 1925. The parents had died at an advanced age. Of the seven brothers and sisters, four sisters were still alive. In the fourth decade of life, the patient suffered for six years with rheumatism of the joints. She had one child. As a result of frequent prolonged standing while she was working as a cook, varices developed on both legs, and since the age of 32, she had had ulcers on the right leg; since her thirty-ninth year, ulcers had been present on the left leg also. For eleven years she was treated for the ulcers with zinc paste bandages, but the ulcers always broke down. Then for a number of years the patient treated the ulcers with applications of phenol solution, for just how long she could not state. Finally, because of continual confinement in bed, she was admitted to the hospital.

Physical Examination.—The patient had a small and delicate frame, which showed fair development and nutrition. The skin and mucosae were generally pale. Edema or exanthems were not present. On both ears over the cartilages, there was a striking bluish-gray coloration, which shimmered through when looked at from the inner surface. On each eye, there were two bluish-black spots beside the corneas. The organs of the neck and throat showed nothing of importance. The cardiac borders were not widened. A systolic murmur was heard all over the precordium, most prominently over the apex. The pulse rate was from 84 to 88, and the rhythm was regular except for an occasional extrasystole. Percussion of the lungs was everywhere resonant, but a few medium coarse moist râles were heard over the bases. The abdomen was soft and flabby and was not tender to palpation. The liver and spleen were not enlarged or tender to palpation. Examination of the urine gave negative results. The upper extremities showed nothing of importance. On both legs, extending from about one and one-half hand breadths below the patella down to the ankles, were ulcers which embraced the circumference of the extremities but which showed fair granulation. The neurologic examination gave negative results.

Course.—Two years later the patient was ill for several weeks, having a slight fever and paratyphosis B bacilli in the stool. Examination of the portio uteri at this time showed a crater-like carcinomatous ulcer, and the uterus was immovable. The patient was discharged on June 30, 1927.

She reentered the hospital a short time later in a marasmic state, and died on Sept. 10, 1927, aged 65.

Autopsy (Professor Pick).—Autopsy was performed on Sept. 10, 1927. The body was that of a small woman of weak bodily frame. General anasarca was present, the edema being quite marked in the arms and legs. The auricles of the ears showed a striking bluish-gray coloration, which was especially prominent in the conchae. Near the cornea of each eye were two bluish-black spots, resembling parentheses. The skin of the face and elsewhere and the visible mucous membranes showed pallor but no pigmentations. On both legs, extending from the middle downward to the ankles and embracing the entire circumference, were ulcers having irregular outlines with firm, stiff borders and smooth reddened bases. When the outer soft tissue of the thorax was removed, the entire cartilaginous tissue of the thorax was seen to appear bluish and to shimmer; this appeared in sharp contrast to the reddish ossified ribs. Ascites were not present. The right diaphragmatic leaf reached to the level of the fourth rib, the left to the level of the fifth rib. In the small pelvis, a hard mass surrounded the firmly walled-in uterus. Both lungs were fixed by numerous flat adhesions. Effusion was not

found in the pleural or pericardial sacs. The heart was of normal size; the chambers were not dilated; the mitral and aortic valves were firm and fibrous and showed light atherosclerotic spots. The musculature was firm and without special significance. The sinuses of Valsalva were markedly widened. At the beginning of the aorta ascendens were calcified plaquelike deposits. The coronary arteries were firm and wide and showed yellowish internal surfaces. Nowhere on the valves, chordae tendinae, or on the intima of the ascending aorta were there pigmentations. The left lung was large and heavy, in places having a lessened air content. On section it was rich in blood and foamy. In the lower lobe posteriorly in a localized area, there was no air; a cloudy fluid exuded on pressure. The bronchial mucosa was reddened. In the main bronchus and its larger branches, there was no evident staining of the cartilage rings. The general condition of the right lung was the same as that of the left. Here, also, in the lower lobe and anteriorly in the upper and middle lobes were atelectatic areas, which on pressure exuded a cloudy fluid. The cartilages of the main bronchus and its branches resembled that of the left, and these were also free from pigmentation. The pharynx, palates, palatine tonsils, tongue, larynx and esophagus were normal. The thyroid was large, and the middle lobe was well developed. The thyroid cartilage showed a striking grayish-blue coloration, as did also the cartilage rings of the trachea.

The spleen was of the usual size and was flabby and slightly firm. On section, it was brownish red, moist and smooth, and the trabeculae were evident. The suprarenals did not show anything of importance. The pelvic organs were removed with the ureters and kidneys. The urinary bladder showed a slight mucosal injection at the base. The mouth of the ureters was patent. In the trigone, the lymph follicles were evident. The middle and the upper third of the vagina, the cervix and the corpus uteri up to the fundus were fully replaced by opaque, grayish-yellow, putrid, disintegrating masses of tumor tissue. In the remaining preserved yellowish portion of the fundus, the muscle wall was 1 cm. thick and contained firm blood vessels. The mucosa showed fresh hemorrhage. Wide flat adhesions covered the fundus uteri, the space of Douglas and the appendages. Both tubes were closed, club-shaped, distended with fluid and flabby and were about the thickness of the small finger. The right ovary was about as large as an almond and densely firm. The left was even smaller. The rectal mucosa was slightly edematous but otherwise free. The left ureter was not especially widened, and its mucosa was pale. The left kidney measured 12.5 by 6 by 3 cm. and was flabby in appearance. The kidney pelvis was extraordinarily widened, having a number of small concrements ranging in size up to that of lentils and having a pale mucosa. The parenchyma was yellowish, and the markings were poorly seen. The right ureter was as thick as a finger; its mucosa was like that of the left. The right kidney measured 10.5 by 5 by 2.5 cm. Here the pelvis was also greatly dilated and had a pale mucosa. The cortex was narrow and had poor markings. The stomach showed old scars in the middle of the small curvature; its mucosa was otherwise free. The extent of the ligamentum hepatoduodenale was free. The liver measured 25 by 17 by 5 cm. and was flabby but somewhat firm; the lobules were large and had sunken centers which were reddish while their peripheries were yellowish. The pancreas and the intestines were free.

The aortic and thoracic aorta showed numerous sclerotic spots and calcified plaques. The plaques in the arch were surrounded by areas of grayish coloration; the abdominal aorta was like the thoracic aorta but without visible areas of pigmentation.

The pia mater and its blood vessels at the base of the brain were delicate. The brain was pale and slightly moist. In the right lenticular nucleus was an elongated area of softening about twice the size of a hemp seed. The vertebral column was removed and after being sawn through the middle, did not show striking pigmentation.

Anatomic Diagnosis.—The condition was diagnosed as disintegrating carcinoma of the vagina, cervix and fundus uteri and bilateral hydrosalpinx. Old adhesions of the uterus and its adnexae, widening of the ureters and bilateral hydronephrotic kidneys, fibrosis and atherosclerosis of the mitral and aortic valves, widening of the sinuses of Valsalva, numerous old pleural adhesions, hyperemia and edema of the lungs, hyperemia of the bronchial mucosa, bronchopneumonia of the left lower lobe and of all the lobes of the right lung, atherosclerosis and calcification of the aorta, a small area of softening in the right lenticular nucleus, old scars of the mucosa of the stomach, slight edema of the rectal mucosa, general anasarca and large circular callous ulcers of both legs were found.

Ochronosis of the cartilage of the ears and ribs, the thyroid cartilage, cartilage rings of the trachea and the main bronchi and ochronotic spots in both sclerae and about the calcified deposits in the intima of the aortic arch were also found.

The bony and cartilaginous tissues that were removed were then studied more minutely.

(1) Sternum, Cartilaginous and Bony Parts: The generally bluish shade of the cartilage of the ribs became changed to a dark gray after removal of the perichondrium. On this dark gray background, there appeared a great number of small dark brown spots which increased in size up to that of a lentil and which in many instances also became confluent. Under the surface and toward the depth the cartilage was pigmented in all directions and was diffusely grayish brown to brown.

(2) Larynx and Respiratory Passage (fig. 1): The thyroid cartilages, covered with perichondrium, showed a blue shimmer. On section (see left thyroid cartilage in figure 1) they were brown. The cartilage rings of the trachea, freed of perichondrium, showed a play of various colors. In part they were brownish yellow to yellow, in part light to dark brown with irregular arrangement of this shade. On cross-section also, the dark brown predominated.

(3) Joints: (*a*) Shoulder joints. The heads of both humeri were smoky gray and showed a somewhat darker shade only toward the border of the surface of the joint. In about the middle of the head of each joint there was a smaller collection of irregular spots. The cartilage itself was smooth. The surface of the joints on both shoulder blades was grayish brown; in the center there was speckling of dark brown spots about twice the size of a lentil, while toward the border of the under surface of the joint there was grayish-brown pigmentation. The brownish color was well seen on cross-section at the point of attachment of the tendons. The cartilage and the intercartilaginous substance of the sternoclavicular joint were light brown. The cartilage eleswhere was without change. (*b*) Hip joints. The cartilage of the heads of the femurs was dark grayish-brown, especially about the attachment of the ligamentum teres, where the spotting was darker bluish and in places grayish black, particularly about the cartilage border. In general the cartilages were smooth, but here and there they had a slight superficial rawness, especially about the point of attachment of the right ligamentum teres, but not about that of the left side. (*c*) Knee joints. Both knee joints showed a diffuse brownish shade of the cartilage and dark gray spotting on the menisci and the cruciate ligaments. The latter were spotted brownish on cross-section. On the

Fig. 1.—Fresh specimen showing ochronotic pigmentation of the thyroid, tracheal and bronchial cartilages.

Fig. 2.—Head of left femur showing distribution of the pigment.

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cartilage of the knee joint a darker spotting on the brownish substratum was present in places. The cartilage everywhere was smooth.

For the microscopic examination of the cartilage, only those specimens could be used in which frozen sections could be made without previous decalcification in nitric acid, since the nitric acid lends a diffuse yellowish tone to the tissue. In this way the examinations were carried out on flat little disks removed from the heads of the femurs and on little pieces of cartilage from the ear. The intactness of the cartilage and also of the ground substance was seen microscopically. The ground substance was pigmented with lighter intensity, varying in color from yellowish to brownish. Granular pigmentation was not found.

Treatment of the sections with 2 per cent silver nitrate solution for three days caused a darker browning; treatment for four days with 3 per cent hydrogen peroxide solution removed the color from the sections completely. One of the darker spots of the sclera was also investigated, and here also the staining of the bundles in the sclera was diffusely light brownish yellow, without deposition of the granular pigment.

The new growth in the uterus was shown to be a simple carcinoma.

The chemical examination (Dr. Brahn) was so carried out that the broken up pieces of stained cartilage from the rib were first treated with 5 per cent cold sodium hydroxide solution to extract the pigment. The staining material did not go into solution. The sodium hydroxide solution was then strengthened to 10 per cent and the mixture warmed for a considerable time on the water bath, centrifugalized, and after dilution with water, filtered. The filtrate was precipitated with concentrated sulphuric acid, giving a faint yellowish-brown deposit.

CLINICAL FEATURES

Alkaptonuria is an endogenous disease occurring in families in which there has been inbreeding, particularly when the parents are cousins (Umber and Buerger[8]). Alkaptonuric ochronosis occurs most frequently in persons in the fifties, although cases have been reported in patients of 23, 30 and 31 years of age.

The clinical diagnosis is made on the presence of pigmentation of the skin, urinary manifestations and the history. In alkaptonuric ochronosis, the examination of the urine confirms the diagnosis. In carbolochronosis, there is a history of long-continued use of carbolic acid washes or dressings. In ochronosis of both groups the external pigmentation may be found in the skin of the face, axillae, hands, the sclerae, the mucosa of the lips and the cartilages of the nose, eyelids and ears. The sweat and cerumen may be stained brownish to blackish. The pigmentation of the face is usually described as yellowish brown and that of the auricles light gray brown to dark blue. Each cornea may be embraced on either side by a group of thickly set, bluish-black, sharply demarcated spots, in form sugggesting parentheses. The cartilages may be stained yellowish brown to grayish blue, and even as black as coal, ebony wood or ink. In carbolochronosis, the cartilages are apt to be less intensely

8. Umber and Buerger, M.: Alkaptonurie mit Ochronose und Osteo-Arthritis deformans; Zystinurie, Deutsche med. Wchnschr. **39**:2337, 1913.

stained. In general the pigment of carbolochronosis is less intense than that of the endogenous form, as is to be expected, since the endogenous form exists through the whole lifetime, whereas the exogenous form is the result of an action occurring a number of years and usually beginning in midlife.

The urine may be dark when it is voided or may become dark after a varying period of exposure to the air. Copper solutions are sometimes reduced. In alkaptonuria the alkapton body may be detected, while phenol and phenol derivatives have been found in the urine in some cases of carbolochronosis. Pick stated that in cases of ochronosis in which the condition is more or less limited to the internal tissues, the finding of ochronotic casts in the urine should establish the diagnosis.

In addition, changes in the joints and the constant finding of cardiovascular lesions have been associated with ochronosis. In alkaptonuric ochronosis, destructive changes in the larger joints and spine are frequently present, particularly arthritis deformans, while in carbolochronosis, changes in the joints have been described but are less constant and seldom severe. In the former type of ochronosis, the condition usually begins to develop in the joints of patients in the forties, while in the latter type, most patients first begin the use of phenol appplications in the forties. This may be the reason for the lesser frequency of arthritic changes in carbolochronosis. Kolaczek[9] reported the occurrence of ochronotic nodes on the tendons of the foot.

The constant association of arteriosclerosis with the frequent occurrence of endocarditis has been mentioned by most writers and would seem to be more than a mere chance relationship.

The cessation of the introduction of phenol into the body may lessen the intensity of the external pigmentation (Poulsen,[10] Fishberg), lighten the color of the urine and effect an improvement in the "carbol marasmus." On the other hand, Gross and Allard regarded the alkaptonuric ochronosis as "an advancing incurable suffering which, if sufficiently intense and of long enough duration, leads to a marked injury in health."

Examination of the blood may reveal the presence of homogentisic acid, tyrosine, tyrosinase or phenylalanine.

PATHOLOGIC FEATURES

Besides the pigmentation of the skin and the cartilages, the pigment may also be found in the connective tissues (intervertebral disks, synchondrosal menisci, ligaments and tendons), in the intima of the

9. Kolaczek, H.: Ueber Ochronose, Beitr. z. klin. Chir. **71**:254, 1910.

10. Poulsen, V.: Ueber Ochronose bei Menschen und Tieren, Beitr. z. path. Anat. u. z. allg. Path. **48**:437, 1910.

aorta, in smooth, striated as well as in cardiac muscle and in the epithelial cells, either as a diffuse or as a granular deposit.

Skin.—A brownish yellow pigment is deposited in the stratum germinativum of the skin epithelium.

Sclera.—There is a difference of opinion among various authors as to whether the pigment is collected in the ocular connective tissue or in the sclera. My observations have shown that the pigment is in the sclera.

Cartilages.—The thyroid, cricoid, tracheal and bronchial cartilages as well as those of the ears, nose, eyelids, ribs and joints are effected. In unstained microscopic sections of cartilage from the ribs, the pigment is yellowish, diffuse or granular and is most intensely deposited immediately beneath the perichondrium and little in the central cartilage. Because the most concentrated deposits of pigment take place at the locations in which the cartilage is most closely bordered by the blood vessels or immediately beneath the perichondrium, Pick has formulated his "basic law for ochronosis pigmentation" in explanation of this distribution.

Connective Tissues.—The patellar ligament may show smoky gray to brownish gray pigmentation, while the intervertebral disks and ligaments, as well as other tendons and connective tissues, may also show the deposition of pigment.

Vascular System.—Changes in the vascular system have been present in all the reported cases that have come to autopsy. Besides the presence of arteriosclerosis, which may be ascribed in part to the age of the patients, endocarditis was present in a number of cases. In one instance Pick found blackish pigmentation on the valves of the heart; diffuse brownish gray and grayish black pigmentation in the intima of the aorta and iliac arteries; blackish collections of pigment about the calcium plaques and blackish streaks in the smooth places. Kolaczek spoke of the condition of the heart and blood vessels as an index to the severity of the ochronosis, and since Virchow's time it has been repeatedly confirmed that the ochronotic pigment binds itself on to the arteriosclerotic lesions in the heart and blood vessels.

Kidneys.—Pick described various changes in the kidneys: diffuse yellowish brown shades of the epithelial parenchyma; tiny cysts which correspond mainly to segments of urinary canaliculi with blackish or colorless content; ochronotic infarcts of the pyramids; coal-black, hard ochronotic concrements in the pelvis, and ochronotic casts filling the tubuli recti, appearing hyaline or granular and staining light bluish with hemalum. Allard and Gross [11] also described black ochronotic concrements in the kidney pelvis.

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11. Allard, E., and Gross, O.: Untersuchungen ueber Alkaptonurie, Ztschr. f. klin. Med. **64**:359, 1907.

Joints.—The arthritic changes are varied and chronic, being variously designated as chronic arthritis, arthritis ulcerosa sicca, arthritis adhaesiva ankylopoetica and arthritis deformans. Benecke called attention to "the typical dry destruction of the degenerating joint cartilages." He characterized the splintering up of cartilage into little spearlike pieces as peculiar to chronic arthritis of alkaptonuric ochronosis, stating that it does not occur in other forms of arthritis. Arthritic changes, however, have been reported in carbolochronosis also, but thus far these changes have not been of an extreme type. The changes in the joints in ochronosis have been likened to those of gout, homogentisic acid being deposited in the joints in the one case and uric acid in the other.

Kolaczek showed that the places in the cartilages that stained most intensely were likewise the most severely damaged. Landois,[12] Allard and Gross and Kolaczek regarded the deposition of the staining material in the cartilages as the etiologic factor for the arthritis. Fishberg called attention to the fact that the arthritis does not depend on the ochronosis but rather on the homogentisic acid or the hydroxylated phenol derivative.

The arthritic and atherosclerotic changes and those in the tendons may therefore all be connected to the homogentisic acid circulating in the blood. According to Pick, the ochronotic pigment has especial attraction for cartilage in the stage of regressive metamorphosis as it generally has for other regressively changed tissue and for vitally weakened cells or for degenerating intercellular substance. The accumulating pigment then increases the injury to the tissue, thus setting up a vicious circle.

MICROCHEMICAL REACTIONS

Pick first accentuated the relationship of the pigment to melanin and showed the two pigments to differ only in a few minor details. The ochronotic pigment is soluble in alkali and insoluble in chloroform; predominantly, it has the characteristics of an acid but is amphoteric to a degree, since it is also slightly soluble in hydrochloric acid. Like melanin, microscopically it does not contain iron; like certain melanins, it does not contain sulphur. Microscopic sections stained with sudan and osmic acid give negative reactions. The pigment bleaches after prolonged soaking in hydrogen peroxide and blackens with certain silver methods, especially well with the method of Bielschowsky.

PHYSIOLOGIC FEATURES

Katsch [13] showed that a series of colors could be produced by various degrees of oxidation of homogentisic acid (by hydrogen peroxide)—

12. Landois, F.: Zur Kenntniss der Ochronose, Virchows Arch. f. path. Anat. **193**:275, 1908.

13. Katsch, G.: Ist ein Ferment defekt Ursache der alkaptonurischen Stoffwechselstoerung? Klin. Wchnschr. **5**:1994, 1926.

straw yellow, pink, red, brown and black. Phenylalanine and tyrosine (von Fürth[14]) have special capacity as color builders. Katsch expressed the belief that various colors can be similarly produced by the action of tyrosinase on tyrosine and homogentisic acid in the body. On this basis, Pick gave his explanation of the genesis and peculiar distribution of the ochronosis. In the genesis of the carbolochronosis, hydrochinon and pyrocatechin are substituted for tyrosine and homogentisic acid in the alkaptonuric ochronosis. The special affinity of the degenerating, and especially of the sclerotic, tissues for the ochronosis pigment may be explained as due to the limited metabolism and sparse oxidation in these places.

SUMMARY

A case of endogenous ochronosis due to long continued application of wet phenol dressings to chronic ulcers of the leg is reported. Special reference is made to the pathologic changes in the bones and cartilages. The various clinical and laboratory features of the different types of ochronosis are enumerated and briefly discussed.

300 Rowena Street.

14. Von Fürth, O.: Physiologische und chemische Untersuchungen ueber melanotische Pigmente, Centralbl. f. path. Anat. u. z. allg. Path. **15**:617, 1904.

OPIUM ADDICTION

I. THE CONDUCT OF THE ADDICT IN RELATION TO INVESTIGATIVE STUDY *

ARTHUR B. LIGHT, M.D.
AND
EDWARD G. TORRANCE, M.D.
PHILADELPHIA

The data to be presented in a series of papers, of which this is the first, have been obtained from studies of persons addicted to opium or its derivatives who have applied for treatment at the Narcotic Wards of the Philadelphia General Hospital. These wards are maintained by the city of Philadelphia and have no relationship to law enforcement agencies. In this introductory paper, we wish to present our impressions of the behavior of the addict for the purpose of emphasizing the existence of obstacles which, if not fully appreciated, may result in failure of investigative efforts. A detailed report of the psychiatric and psychologic studies will be published later by members of the staff investigating this phase of the problem of opium addiction.

REASONS FOR SEEKING TREATMENT

The person who presents himself for treatment in these wards does so of his own volition and for one or more of the following reasons: He is disgusted with his slavery to the drug; he desires temporary refuge from the police, or for financial reasons he wishes to reduce the amount of his daily dosage or to obtain free maintenance for a time. Regardless of the motive for seeking treatment, patients who apply for admission either have had an unusually large dosage (as they express it, are well "shot-up") or are manifesting early withdrawal symptoms. In either event, they will agree to any sort of experimentation as long as it promises their immediate or early acceptance for treatment. This apparent desire on their part to cooperate must not be taken seriously, as we will point out later.

RELATIONSHIP TO DRUGS

After a person has become firmly addicted to the use of opium or one of its derivatives, we have reason to believe that the problem of

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* From the Narcotic Wards of the Philadelphia General Hospital.

* Expenses of this research were defrayed by the Committee on Drug Addictions, New York City. The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

securing and maintaining an adequate supply of the drug comes to be the major purpose of his existence. To an extraordinary degree, he develops a sagacity and persistence in this direction which may outmatch the abilities of those who are conducting the investigation. The ingenuity that is displayed in maintaining channels of supply is amazing. We have come to believe that practically every word which the addict utters and every deed which he may perform are based directly or indirectly on a motive concerned with the maintenance of these channels of supply. He will plead with or threaten those about him who are in a position to supply him with the drug. Whatever method he may use has been previously determined by careful consideration on his part as to which may be the more successful.

Undoubtedly there are some who desire to give up the drug on account of disgust and give this reason in all sincerity. The patients encountered in the wards of the Philadelphia General Hospital are practically all from the so-called underworld. A considerable number of them have, however, at one time lived in better circumstances. Not any of them has fallen so low as to fail to realize that he is an outlaw under present conditions of the law and public opinion. This realization together with the undoubted tax on their mental processes levied by the very ingenuity which these persons display is enough to bring about this so-called disgust with the drug. This feeling, however, quickly vanishes when the addict is confronted with the sufferings attendant on failure of supply of his drug.

GENERAL BEHAVIOR IN THE WARD

After admission to the ward with the knowledge that the drug is available and will be supplied for certain lengths of time, the addict becomes amenable. His behavior is excellent, and he desires to cooperate in any experiment which does not interfere with his daily dosage. This cooperative attitude on the part of the addict is real and sincere but lasts only as long as the effects of the drug persist, usually a matter of hours. When the effects of the drug pass off, all the sagacity and ingenuity on his part are brought into play as only those who have been associated with this type of person can appreciate.

Not only must the observer forstall the schemes which the addict is devising to obtain the drug, but he must defeat plans, made before admission, for the restoration of his supply should his craving become unbearable. He may have attempted to bring the drug into the ward concealed in his clothing, letters, jewelry or in any orifice of the body large enough to hold it. Extreme care must be taken to search the addict before admission. We have found drugs concealed in the soiled dressings covering abscesses resulting from infections caused by hypodermic injections.

Should his attempts to bring a certain quantity of the drug into the ward have failed, he resorts to plans devised to obtain it from friends outside of the hospital, or he schemes with fellow addicts who are about to be discharged and who have signified their intentions to him of immediately returning to the use of the drug. He will attempt to bribe any one who appears open to temptation. Letters will come addressed to him which have been written on paper previously saturated with the drug, dried, ironed out and then inscribed with a harmless message. He will extract the drug by either chewing the paper or redissolving it in water. Sometimes the drug is concealed under the stamp of the envelop. The wooden stem of a match changed into a cylinder has been found to contain a drug. He will accuse or betray his best friend in order that he may gain favor from those in charge. Telegrams and telephone messages will arrive bringing the news of the death of a member of the family, asking his immediate return home. These are but a few of the methods employed to obtain drugs, and unless forestalled they will ruin any studies made during the withdrawal period. In addition, there is always danger that the patient may be aided by a fellow addict who may have drugs in his possession, or by a drug pedler who will furnish drugs without charge when it insures him the return of the addict with funds in the near future.

Practically 80 per cent of the addicts appearing for treatment were using heroin before admission to the wards. The rest were addicted to morphine, except one or two who used camphorated tincture of opium and tincture of opium. In the cases of morphine and heroin addiction, the hypodermic method of administration was the choice, except in several cases of sniffing and in two in which self-intravenous administration was employed. After admission to the ward, all persons used for study were supplied with drugs in the form of morphine administered hypodermically. Enough of the drug was given to allay any possible suffering. We find that morphine easily displaces heroin in maintaining comfort and rest. All studies to be reported must be considered as studies made during morphine addiction and morphine withdrawal.

While the person is under the influence of the narcotic, his behavior is normal. Not having much to do, he spends his time smoking cigarets and engaging in conversations, chiefly on drug addiction. As a rule, the addict is interested in sporting events and the latest newspaper scandals. Although supplied with fiction of the lighter variety, he is not a consistent reader while in the ward. He eats well, sleeps well and helps to keep the ward clean, lending a helping hand to any kind of work requested. He is docile, well behaved and is altogether easy to deal with while receiving the drug and while desiring to remain in the ward.

WITHDRAWAL SYMPTOMS

The withdrawal of the drug results in a striking change in the appearance and behavior of such a person. The symptoms which make their appearance have frequently been described in the literature (Johnson,[1] Levinstein,[2] Sollier,[3] Morat,[4] Bishop[5] and Lambert[6]). Having studied their onset carefully, we shall describe them briefly in the order of their appearance as we have observed them.

As the time approaches for what would have been the addict's next administration of the drug, one notices that he glances frequently in the direction of the clock and manifests a certain degree of restlessness. If the administration is omitted, he begins to move about in a rather aimless way, failing to remain in one position long. He is either in bed, sitting in a chair, standing up or walking about, constantly changing from one to another. With this restlessness, yawning soon appears, which becomes more and more violent. At the end of a period of about eight hours, restlessness becomes marked. He will throw himself onto a bed, curl up and wrap the blankets tightly around his shoulders, sometimes burying his head in the pillows. For a few minutes he will toss from side to side and then suddenly jump out of the bed and start to walk back and forth, head bowed, shoulders stooping. This lasts only a few minutes. He may then lie on the floor close to the radiator, trying to keep warm. Even here he is not contented, and he either resumes his pacing about or again throws himself onto the bed, wrapping himself under heavy blankets. At the same time he complains bitterly of suffering with cold and then hot flashes, but mostly chills.

He breathes like a person who is cold, in short, jerky, powerful respirations. His skin shows the characteristic pilomotor activity well known to these persons by the name of "cold turkey." The similarity of the appearance of the skin at this stage to that of a plucked turkey is striking. Coincident with this feeling of chilliness, he complains of being unable to breathe through his nose. Nasal secretion is excessive. He has a most abject appearance, but is fairly docile in his behavior. This is a picture of his appearance during the first eight hours.

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1. Communication from G. H. Smith, Esq., to Dr. Johnson, Lancet **1**:707, 1841-1842.

2. Levinstein, E.: Die Morphiumsucht, 1878, p. 14.

3. Sollier, P.: La demorphinisation et le traitement rationel de la morphinomanie, Semaine med., 1894, p. 146.

4. Morat, D.: Le sang et les secretions au cours de la morphinomanie et de la desintoxication, These de Paris, 1911.

5. Bishop, E. S.: Narcotic Addiction: A Systemic Disease Condition, J. A. M. A. **60**:431 (Feb. 8) 1913.

6. Lambert, A.: Nelson's Looseleaf Medicine, 1920, vol. 2, p. 607A.

Often at the end of this period, the addict may become extremely drowsy and unable to keep his eyes open. If he falls asleep, which is often the case, he falls into a deep slumber well known as the "yen" sleep. It takes unusual noises to awaken him. The sleep may last for as long as eight or twelve hours. On awakening, he is more restless than ever. Lacrimation, yawning, sneezing and chilliness are extreme. A feeling of suffocation in the back of the throat is frequently mentioned. Usually at this stage, the addict complains of cramps, locating them most frequently in the abdomen, but often in the back and lower extremities. A right rectus rigidity with pain localized over the appendical region is not uncommon; one can easily be misled in the diagnosis, since at this stage a leukocytosis is frequently present, as will be pointed out in a later paper. Vomiting and diarrhea appear. He may vomit large quantities of bile-stained fluid. Perspiration is excessive. The underwear and pajamas may become saturated with sweat. Muscular twitchings are commonly present; they may occur anywhere, but are most violent in the lower extremities. He may sit in bed with his leg flexed, grasping it tightly below the knee, fearing the twitch which will suddenly throw it into complete extension and which he cannot control. If he is handed a cigaret to smoke, his hand trembles so violently that he may have difficulty in placing it in his mouth. The tremor is so marked that he is unable to light it himself.

He refuses all food and water, and frequently sleep is unknown from this point. It is at this stage that he may one minute beg for a "shot" and in the next minute threaten physical violence. Nothing can make him smile. He will beat his head against the wall or throw himself violently on the floor. Any behavior which he thinks may bring about the administration of the drug will be resorted to. Occasionally he may complain of diplopia. Seminal emissions in the male and orgasms in the female frequently occur.

We believe that the height of these withdrawal symptoms is reached somewhere between the period of forty-eight and seventy-two hours following the last dose of the drug taken. The readministration of the drug promptly brings about a dramatic change. The patient becomes exceedingly docile almost simultaneously with the puncture of the hypodermic needle. In a few minutes he begins to feel warm, and the gooseflesh and perspiration are no longer visible. He speaks about a "heaviness" in his stomach, but regards this as a welcome symptom presaging relief. In a period ranging from thirty minutes to one hour, the muscular tremors disappear. He has become strong and well. He no longer walks with bowed head and stooped shoulders. He stands erect, is quite cheerful and lights his cigaret like any normal person. He becomes profuse in his apologies for his conduct during the abrupt withdrawal of the drug.

The intensity of some of these symptoms is undoubtedly subject to control on the part of the patient. We have stated that his mode of behavior is governed largely by his attempts to impress his suffering on those observing him. On the other hand, if there is a possible chance of obtaining his liberty from the ward he will state, though feeling ill, that he "feels fine," "has an excellent appetite" and is "sleeping well." He may have been successful in smuggling and administering the drug to himself and yet feign withdrawal symptoms so as to allay suspicion. When it is time for his discharge, he may feel well from the effects of the drug that he has been able to obtain through smuggling.

UNRELIABILITY IN RELATIONSHIP TO STUDY

This control of his symptoms on the part of the patient must be thoroughly understood by those engaged in the employment of various sorts of treatment. We believe that in many cases false conclusions are drawn as to the efficacy of a treatment if the value is deduced from the statements of the patient and his appearance. The scopolamine treatment that we have employed has always been stated by the patient who has been previously treated and who wishes to enter the ward to be "the best he has ever undergone, all others being torture." When he is just recovering from the effects of the scopolamine, it is "the worst," all others being excellent. When the time approaches for his discharge and he is anxious to obtain his liberty, the treatment again becomes the most successful he has ever had; he appears to have fully recovered his normal strength when he may still be so weak that he may not be able to walk several blocks without collapsing.

CONCLUSIONS

We have attempted in this paper to give a picture of the opium addict as we have found him in the wards of the Philadelphia General Hospital. We believe this description to be essential so far as it points out the difficulties encountered in the study of human addicts. Without this introductory paper, the reader might fail to appreciate in the papers which are to follow, the deceptiveness of the addict during experimentation.

THE RADICULAR SYNDROME IN HYPERTROPHIC OSTEO-ARTHRITIS OF THE SPINE

AN ANALYSIS OF THIRTY CASES*

LEWIS GUNTHER, M.D.
AND
WILLIAM J. KERR, M.D.
SAN FRANCISCO

Thirty-five years ago von Bechterew [1] wrote the first of a series of papers which described a syndrome consisting of stiff spine, nerve root pains, nerve root degeneration, alterations of sensation and muscle atrophies of a radicular distribution, which he ascribed to a pachymeningitis and compression of the nerve roots. Following the descriptions of Strümpell [2] and Marie,[3] much discussion ensued on the classification of the various types of spondylitis, and with the exception of the work done in France and the reports by Camus,[4] Leri,[5] Sicard [6] and Barré,[7] the neurologic side of the syndrome has received little attention.

In the English and American literature, references to the radicular syndrome have been few indeed, and under this title reference had not been made to spinal osteo-arthritis as the causative agent, until the appearance of Rosenheck's [8] contribution in 1924, on radicular pain in spondylitis deformans. Well known textbooks [9] and systems of

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1. Von Bechterew, W.: Steifigkeit der Wirbelsäule und ihre Verkrümmung als Besondere Erkrankungsform, Neurol. Centralbl. **12**:426 (July 1) 1893.

2. Strümpell, A.: Bemerkung über die chronische ankylosirende Entzündung der Wirbelsäule und der Hüftgelenke, Deutsche Ztschr. f. Nervenh. **11**:338, 1897.

3. Marie, Pierre: Sur la spondylose rhizomelique, Rev. de méd. **18**:285, 1898.

4. Camus, P.: Étude de neuropathologie sur les radiculites, Thèse de Paris, 1907-1908, p. 26.

5. Leri, André: La radiculite cervicale simple ou "Rhumatismale," Bull. et mém. soc. méd. d. hôp de Paris **40**:686, 1916.

6. Sicard, J. A.: Névrodocites et funiculites vertebrales, Presse méd. **26**:9 (Jan. 7) 1918.

7. Barré, J. A., and Gunsett, A.: Resultat de la radiothérapie dans 20 cas de radiculite par arthrite vertèbrale (et en particuliere dans la sciatique lumbosacrié), J. de radiol. et d'électrol. **5**:492, 1921.

8. Rosenheck, C.: Radicular Pain and Its Relation to Spondylitis Deformans from a Neurological Standpoint, M. J. & Rec. **120**:215, 1924.

9. Osler, Sir William, and McCrae, T.: The Principles and Practice of Medicine, ed. 9, New York, D. Appleton & Company, 1923. Jelliffe, S. F., and White, W. A.: Diseases of the Nervous System, Philadelphia, Lea & Febiger, 1923, p. 445.

medicine have rarely included the radicular syndrome or radiculitis in their indexes, but when included, the relation to osteo-arthritis of the spine has not been mentioned. Under discussions of spondylitis and of osteo-arthritis, Rhein [10] reported pathologic changes in nerve roots in a case of spondylose rhizomelique (P. Marie); Bailey and Casamajor [11] and also Parker and Adson,[12] noted pain and objective sensory disturbances from nerve root and cord compression; Danforth and Wilson,[13] observed the radicular nature of sciatica, and Rosenheck,[14] called attention to so-called meralgia paraesthetica as a radicular manifestation. Osler,[15] under the heading of spondylitis, quoted von Bechterew's original observations, and McCrae,[16] in the Oxford System of Medicine, stated that "sensory changes are important," but, like many other writers, he left the reader rather doubtful regarding their nature and distribution.

Radiculitis may be described as an acute inflammation of the spinal nerve roots, manifested by alterations of sensation or of changes in muscle function, which show by their distribution that the primary disease process is in the spinal root and not in the tracts and nuclei of the cord, or in a peripheral nerve trunk. Dejerine [17] considered syphilis and tuberculosis the most common etiologies. Spinal osteo-arthritis as a cause of radiculitis received little attention.

A root type of altered sensation or of changed motor power is not distinctive in itself, because a similar picture may be produced in many diseases of the spine. That radiculitis may result from osteo-arthritis of the spine and is due to involvement of the nerve root, either from the meningeal reaction secondary to the osteo-arthritic process, or from pressure in narrowed canals, has been shown experimentally by Nathan,[18]

10. Rhein, J. H. W.: Pathologic Report of the Nervous System in a Case of Spondylose Rhizomelique, J. A. M. A. **51**:463 (Aug. 8) 1908.

11. Bailey, P., and Casamajor, L.: Osteoarthritis of the Spine as a Cause of Compression of the Spinal Cord and Its Roots, J. Nerv. & Ment. Dis. **38**:588, 1911.

12. Parker, H. L., and Adson, A. W.: Compression of the Spinal Cord and Its Roots by Hypertrophic Osteoarthritis: Diagnosis and Treatment, Surg. Gynec. Obst. **41**:1, 1925.

13. Danforth, M. S., and Wilson, P. D.: Anatomy of the Lumbo-Sacral Region in Relation to Sciatic Pain, J. Bone & Joint Surg. **7**:109, 1925.

14. Rosenheck, C.: Meralgia Paraesthetica: Relation to Osteo-arthritis of Spinal Vertebrae, J. A. M. A. **85**:416 (Aug. 8) 1925.

15. Osler (footnote 9, first reference).

16. McCrae, Thomas: Arthritis Deformans, Oxford Medicine, London, Oxford University Press, vol. 4, p. 390.

17. Dejerine, J.: Semiologie des affections du système nerveux, Paris, Masson & Cie., 1914, pp. 257 and 821.

18. Nathan, P. W.: The Neurological Condition Associated with Polyarthritis and Spondylitis, Am. J. M. Sc. **152**:667, 1916.

and recognized clinically and described by certain French workers,[19] as rheumatic radiculitis, neurodocitis, funiculitis and funicular-radiculitis. But even as late as 1922, Bassoe,[20] in discussing nerve syndromes and osteo-arthritis of the spine as a cause of sciatica, lumbago and cervical, brachial and intercostal neuralgias, called attention to the appalling lack of objective observations.

There are no criteria by which the extrameningeal neurodocitis or funiculitis of Sicard [6] (fig. 1) can be distinguished from the involvement of the intrameningeal portion of the root, since the involvement of either part will be manifested as a radicular disturbance.[21] In this study, therefore, to denote involvement of the spinal nerve roots we shall use the terms radicular syndrome or radiculitis. These will include the extrameningeal funiculitis and intervertebral neurodocitis of Sicard, and the intrameningeal radiculitis of Dejerine.

Mayer [22] indicated that there may not be any demonstrable sensory changes in the early stages of radiculitis, and that later disturbances consist of alterations in light touch. Osteo-arthritis of the spine is a common disease indeed, and from the very nature of the process radicular manifestations with sensory changes to light touch should be present.

ANATOMY

The spinal nerves are joined to the spinal cord by their dorsal and ventral roots, which are frayed-out bundles of axons, called the fila radicularia, at their lines of attachment to the cord. The fila radicularia and the short intrameningeal portions of the roots are called by Sicard the "radicular nerves," as distinguished from the extrameningeal portions which he calls the "funicular nerve" (fig. 1). The dorsal root contains the spinal ganglion (fig. 2), which is closely invested by the dura mater, but is largely outside its cavity.

Although the roots pierce the dura separately, they are enclosed in a single tubular sheath of dura, which includes the spinal ganglion and posterior root, and thus ensheathed, the spinal nerve occupies the intervertebral foramen. The ganglions of the last lumbar and first four sacral nerves lie inside the vertebral canal, but outside the dural sac, while the ganglions of the last sacral and the coccygeal nerves lie not

19. Camus (footnote 4). Leri (footnote 5). Sicard (footnote 6). Barré and Gunsett (footnote 7).

20. Bassoe, P.: Nervous Syndromes: Osteoarthritis of the Spine, Vertebral Funiculitis Neurodocitis, Internat. Clin. **3**:232, 1922.

21. Williams, T. A.: Differential Diagnosis of Radiculitis and Neuritis, Arch. Diagnosis **14**:140, 1922.

22. Mayer, E. E.: Radiculitis: Its Diagnosis and Interpretation, J. A. M. A. **71**:353 (Aug. 3) 1918.

only inside the vertebral canal, but inside the dural sac as well. The two roots leave the intervertebral foramen together as a short trunk which soon breaks up into branches, which in certain regions furnish the elements making up the plexus (fig. 1). The dura is separated from the periosteum and the wall of the intervertebral canal by a very small interval, containing thin-walled plexiform veins and loose fatty connective tissue.[23]

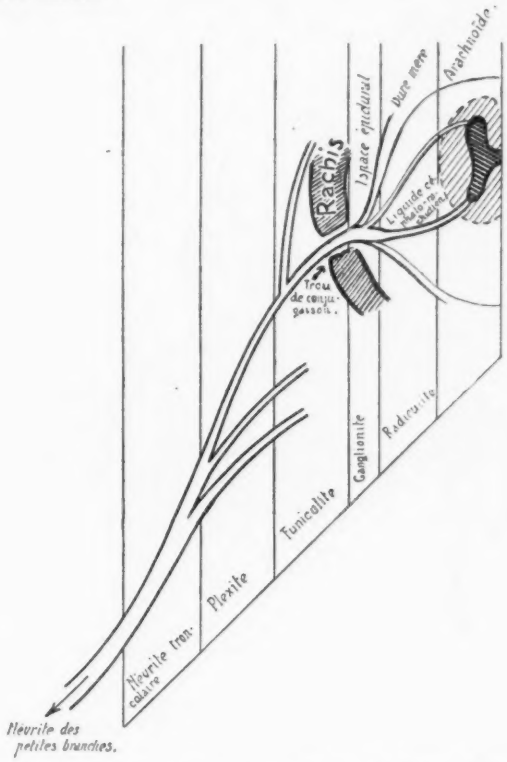

Fig. 1.—Sicard's schematic representation of the spinal roots. He called the fila radicularia and the short intrameningeal portions of the spinal root the "radicular nerve"; the extrameningeal portion the "funicular nerve," and the intervertebral foramen the "neurodocha."

Sicard [6] used the term "neurodocha" to describe the bony canal through which the spinal roots pass to reach their foramina of exit (fig. 1). A pathologic process within the intervertebral canal (the

23. Robinson, Arthur: Cunningham's Text-Book of Anatomy, ed. 5, New York, William Wood & Company, 1923, pp. 711-713.

neurodocha), he called a neurodocitis, and involvement of the short extrameningeal spinal root trunk (the funiculite), he termed a funiculitis. Sensory alterations (or changes in motor power), dependent on a pathologic process in a given nerve root, will be manifested at the periphery as a radicular disturbance (fig. 3), regardless of whether or not the part involved is intrameningeal or extrameningeal.[22]

The spinal roots vary in size. The largest are those that take part in the formation of the great nerve trunks of the limbs, namely, the lower cervical and first thoracic roots and the lumbar and sacral roots.

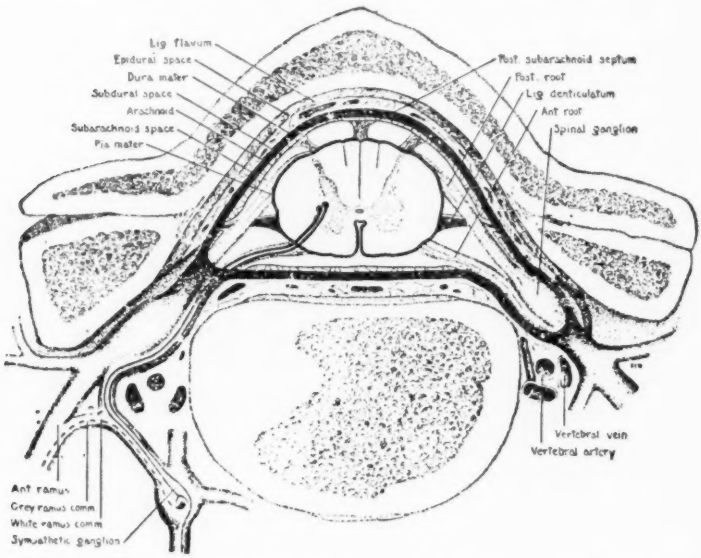

Fig. 2.—The spinal nerve roots and meningeal sheaths. (From Mayer [footnote 22].)

Of these, the nerves destined for the lower limbs are the larger. All the thoracic nerves except the first are small.[23]

The sixth cervical root is the largest of the cervical nerves.[24] These roots diminish in size from below upward.[23] The size of the nerve root in relation to the canal is of definite importance in determining the liability to mechanical irritation. Danforth and Wilson,[13] in a careful study by dissection of the lumbar and sacral nerves, found that beginning with the fifth lumbar root, from below upward, the size of the nerve decreased relatively to the size of the foramen; viz., for their size,

24. Piersol, G. A.: Human Anatomy, Philadelphia, J. B. Lippincott Company, 1907, vol. 2, p. 1279.

the fifth lumbar roots had the smallest canals, frequently almost filling them; the fourth lumbar roots rarely completely filled the foramina of exit, and the second and third lumbar roots never completely filled the openings.

With respect to the size of individual roots, the posterior are larger than the anterior. They contain a greater number of radicular fibers, and the individual fibers are larger.[23] In the cervical region, the posterior

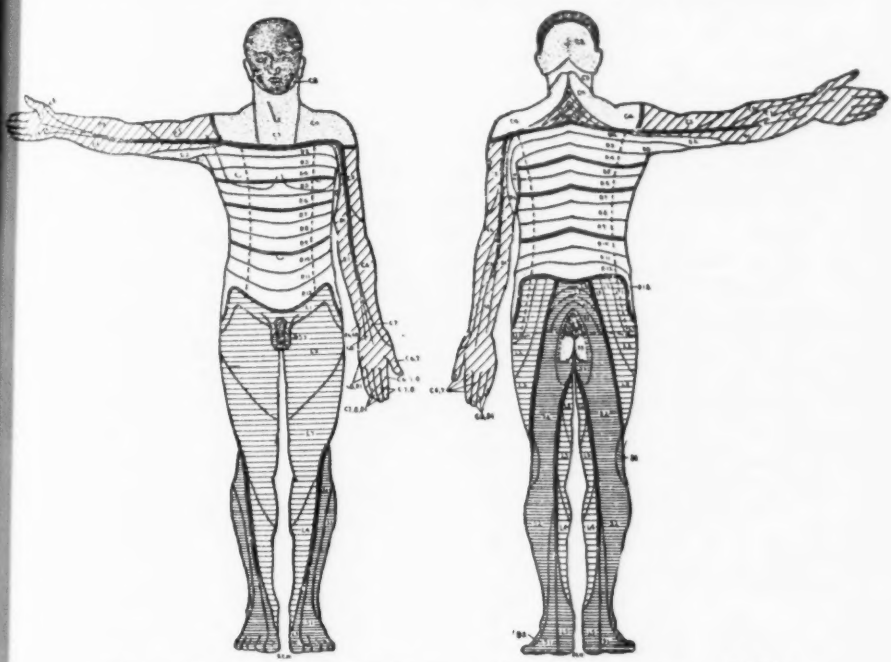

Fig. 3.—The topographic distribution of the spinal nerve roots. Radicular sensory innervation: heavy lines indicate direction or axial lines (modified from Dejerine and Flatau). (From Mayer [footnote 22].)

roots are three times larger than the anterior,[25] except in the case of the first cervical, which is always smaller, and, in rare cases, absent.

The composition of the intervertebral canal and the relation of the roots in this canal are of some importance. The roots are in relation, above and below, respectively, to the inferior and superior intervertebral notches of the adjacent vertebrae; in front, with some of the posterior part of the bodies and with a portion of the intervertebral disk separat-

25. Lewis, W. H.: Gray's Anatomy, ed. 21, Philadelphia, Lea & Febiger, 1924, p. 923.

ing them, and behind, is the posterior articulation. The superior posterior articular facet reaches upward toward the inferior intervertebral notch of the body above, and on movements of extension it approaches the nerve root in the canal and further decreases the size of the intervertebral foramen.[13]

ETIOLOGY, PATHOLOGY AND PATHOGENESIS

Von Bechterew found a pachymeningitis and degeneration of the nerve roots. He considered the neurologic symptoms due to this pathologic condition, with consequent mechanical compression of the nerve roots. Various French writers, Chapault and Raymond (cited by Camus [4]), Leri [5] and Sicard,[6] conformed essentially to this view. Leri, particularly, indicated the possibility of the process being inflammatory. Sicard considered the process periosteal inflammation with secondary involvement of the meninges of the nerve roots in the intervertebral canal. Bailey and Casamajor [11] described in considerable detail the gross pathologic changes of advanced spinal osteo-arthritis, and stressed particularly the thickened root meninges and bony overgrowths from the posterior surfaces of the vertebral bodies and around the intervertebral canal as a cause of compression of the cord as well as the roots. Like their predecessors,[26] they felt that symptoms were produced by mechanical irritation and pressure on the nerve roots in the intervertebral foramen. Rhein [10] found nerve root and muscle degeneration in a case of spondylose rhizomlique (P. Marie). This observation is essentially the pathologic picture described originally by von Bechterew.

In this country, Nathan,[18] by experimental work on dogs and comparative studies of the pathologic changes in man, called attention to the inflammatory nature of the pathologic process in spondylitis deformans. He concluded that subjective and objective sensory alterations of a radicular nature should be present, depending in degree on the severity of the periradicular exudation. The intensity and permanence of these symptoms depended on the fibrosis subsequent to repair after the inflammatory process had subsided. The persistence of neurologic symptoms and signs were due, he thought, to a mechanical disturbance in the spinal canal and in the intervertebral foramen, secondary to these sequellae. Patrick [27] stressed the occurrence of low grade fever and low grade leukocytosis in osteo-arthritic processes. Elliott [28] discussed Nathan's work and the theories advanced as to the etiology of spinal osteo-arthritis.

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26. Bechterew (footnote 1). Camus (footnote 4). Leri (footnote 5).

27. Patrick, H. T.: Neuritis and Sciatica, J. A. M. A., **69**:2176 (Dec. 29) 1917.

28. Elliott, G. R.: Spinal Osteoarthritis Involving Cervical Region, J. Bone & Joint Surg. **8**:42, 1926.

The similar observations of von Bechterew and Rhein in supposedly different types, would indicate that the pathologic condition of the nerve roots was essentially the same in the various forms of spondylitis. Nathan felt that it was unnecessary to classify spondylitis according to the presence or absence of neural symptoms, the mode of progression or the involvement of ribs and joints of the extremities. "Whether or not these parts are involved is merely an accident of location of a generalized process, and such accidental distribution provides the forms commonly associated with the names of von Bechterew, Strümpell, P. Marie, etc. These conditions are not essentially different —like all inflammatory conditions they may be acute, chronic, transient, or progressive, with or without permanent changes to the tissues involved."

Parker and Adson,[12] in a series of patients with nerve root and cord symptoms, who were subjected to exploratory laminectomy, found that the hypertrophic process may be extensive without roentgenologic evidence of its presence. They too concluded that the process was inflammatory, with infection and trauma as the prominent factors. The former they considered the more common and prominent cause of the disease, and the latter the predisposing factor, which continued the process through mechanical irritation.

METHOD OF STUDY

In the medical out-patient department and wards of the University of California Hospital, studies were conducted on patients whose symptoms indicated disturbances of the spinal roots. In the history of the chief complaint, the patients outlined the painful areas lying in a root, or a group of roots, to a degree that was remarkable for its topographic accuracy. When they were questioned, the history brought out that there had been other painful areas of spinal root distribution not complained of at the time. The demonstration of root involvement was equally consistent, when analysis was made of the past history of patients without subjective complaints, in whom moderate to marked hypertrophic changes were found by x-ray examination. In either event, the history of the involvement of various spinal root areas was obtained, and from it a record of involved roots could be formed, which, in most cases, was sufficiently accurate in itself to suggest the levels at which a pathologic process might be anticipated in the spinal vertebrae.

Alterations in sensation to light touch were tested for on all patients by the use of the cotton tuft on a wooden applicator which was approximately 6 inches (15.24 cm.) long. The applicator was held lightly at about its midpoint, and the tufted end was applied to the skin, resting by its own weight without added pressure from the hand. In

a number of patients, tests were conducted with the pinpoint, heat, cold and pinching. One or two painful areas were selected at a given examination, usually that of chief complaint, and other regions were left for a later examination. This procedure was adopted because of the patient's ready fatigue incident to examination for alterations in light touch. Several examinations were necessary if all the involved areas were to be studied.

AGE AND SEX INCIDENCE

Age.—The age incidence of hypertrophic osteo-arthritis of the spine covers a wide range. It is not necessarily a part of old age. The youngest patient in this series showing x-ray evidence of spinal osteo-arthritis was 34, and the oldest was 72. Twenty-three patients were between the ages of 37 and 54, and five patients were over 55.

Sex.—Hypertrophic osteo-arthritis of the spine is considered to be more prevalent in men than in women,[12] the reason given being that in men the spine is subject to more trauma. In this group, the women outnumbered the men two to one. This reversibility may be explained by the attendance figures at the afternoon clinic of the University of California Medical Dispensary, where most of this work was carried on. In attendance, the women outnumbered the men in about the same ratio.

SINGLE SYMPTOMS AND REGIONS INVOLVED

In order of frequency, the chief complaints were: pain, aching, soreness, stiffness, paresthesia (burning, numbness, tingling, heaviness, weight), dizziness, cramps and tenderness. Pain was described as sharp, shooting, gnawing, catching, tender, dull, pinching, twinging, piercing and the like, in various ways, according to the manner of expression of the patient. Aching was of a dull character, and the soreness was either heavy or light. The outstanding symptoms, according to frequency, were: pain, aching, soreness, and stiffness.

The regions complained of (fig. 4), according to frequency, were: (1) an area immediately over the sacrum with sciatic radiation (fig. 4*A*); (2) localized pain over the sacrum, with concomitant pain on the inner side of the legs (fig. 4*B*); (3) an area over the back of the neck (fig. 4*C*); (4) the side of the neck and shoulders (fig. 4*D*); (5) over the occiput and vertex (fig. 4*F*); (6) the upper part of the abdomen and the epigastrium, with radiation to the back (fig. 4*G*); (7) the lower part of the abdomen, with radiation to the back, or from the back (fig. 4*H*); (8) the precordium with radiation to the inner part of the left arm (fig. 4*I*), and (9) the outer side and front of the thigh (fig. 4*J*). Although the patients complained of pain on one side more than on the other, bilateral involvement was most frequent, the right side receiving more attention in the abdomen and

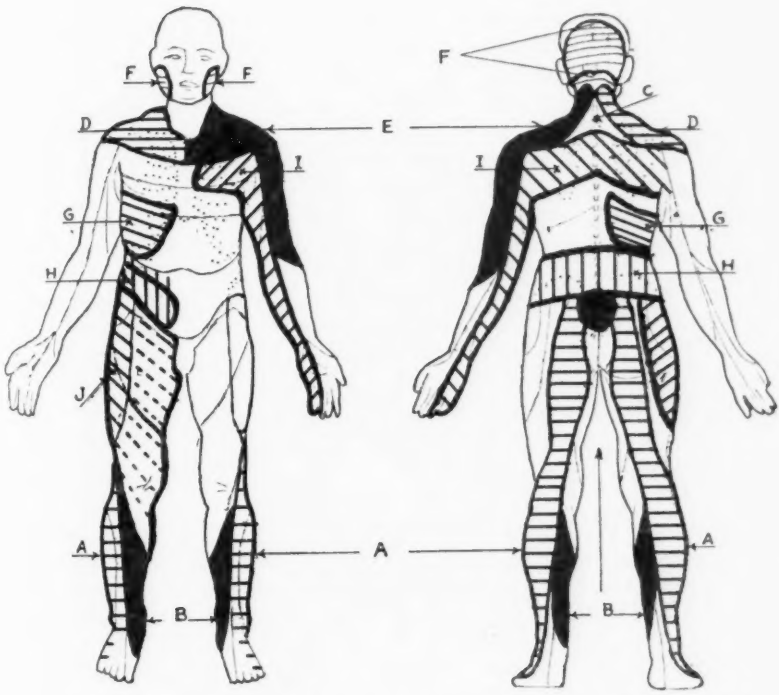

Fig. 4.—*A*, the radicular distribution of the sacral roots 1 and 2, "sciatica." *B*, the radicular distribution of the lumbar roots 4 and 5 and the sacral root 1 over the sacrum (backache) and the radicular distribution of the lumbar root 4 on the "inner side of the legs." *C*, the radicular distribution of the cervical roots 5, 6 and 7 over the area "up and down the back of the neck." *D*, the radicular distribution of the cervical root 4 over the "side of the neck" and the "shoulder." *E*, the radicular distribution of the cervical root 4 and radiation "over the arm" found when areas *D* and *E* were affected concomitantly. *F*, the radicular distribution of the cervical roots 1, 2 and 3 over the back of the head and neck and on the face. Spoken of as "headache" by the patient, occipital and vertex. *G*, the radicular distribution of the dorsal roots 6, 7, 8 and 9, the area of referred pain in disease of the gallbladder. *H*, the radicular distribution of the dorsal roots 10, 11, and 12, the area of referred pain and local tenderness in appendicitis; also backache over the "small of the back." *I*, the radicular distribution of the dorsal roots 1, 2, 3, 4 and 5, the area of referred pain in certain cardiac diseases. *J*, the radicular distribution of the lumbar roots 1, 2 and 3 on the outer side of the thigh (may be confused with meralgia paraesthetica) and across the front and inner side of the thigh.

the left side over the upper part of the chest. Questioning was sometimes necessary to bring out the bilateral nature of the symptoms.

The roots which make up the great nerves of the lower and upper extremities were outstandingly involved, when the location of the symptoms was noted according to their frequency. The involvement of the roots supplying the lower extremities was somewhat more frequent than of those to the upper extremities. The incidence of involvement ment can be explained by anatomic facts. The roots forming the great nerve trunks of the lower extremities are the largest of all the spinal roots. Those supplying the cutaneous distribution of so-called sciatica, the fourth and fifth lumbar and the first two sacral roots, are most frequently subjected to mechanical irritation or compression owing to narrowed canals caused by arthritis of the fourth and fifth lumbar vertebrae, and of the lumbosacral and sacro-iliac joints.[13] The less frequent radicular symptoms and sensory changes in the upper lumbar roots in this series of cases may be explained by the fact that the first, second and third lumbar roots rarely fill their containing canals by one half and are, therefore, less apt to be affected by processes tending to decrease the relative size of the intervertebral canal.[13]

In the cervical region, symptoms referable to the lower cervical roots were twice as frequent as those to the upper. This may be explained by the diminishing size of the cervical roots from below upward, the sixth cervical root being the largest.[24] The nature of the cervical curve and the greater mobility of the lower cervical vertebrae increased the liability of these roots to mechanical irritation.

In the abdomen, symptoms over the right upper and right lower quadrants received more attention than the corresponding left quadrants. The dorsal roots are small; everything else being equal, the greater mobility of the lower dorsal vertebrae enables mechanical trauma to play a greater rôle in the corresponding dorsal roots. Education of the laity, by the medical profession, and by surgeons in particular, concerning diseases of the gallbladder and the appendix, has perhaps caused attention to be focused on these regions, for, despite bilateral symptoms, the patients seemed more concerned with disturbances on the right side of the abdomen. That the location of a known organ draws attention to one side of the body is well illustrated in the upper part of the chest where the painful area, in the proximity of the heart, attracted overwhelming attention to the left side. There was a tendency to minimize the pain on the right side of the chest. When a patient was asked if he would seek a physician because of pain on the right side, such as he now felt on the left side, it was quite characteristic to have him reply: "I would pay no attention to it because the heart is not on that side."

THE COMMON SYMPTOMS IN THE INVOLVED REGIONS

Fingers.—Paresthesias were the main symptoms. These, in order of frequency, were: tingling, numbness and anesthesia. They were associated with the involvement of the lowermost cervical and the upper dorsal vertebrae.

Head.—Headache was the chief complaint. It was usually described as a dull ache, soreness or burning, at the occiput, which shot most commonly to the vertex, and less frequently around the side of the head to the temples. The subjective sensations at the vertex were those of piercing pain, tenderness, soreness, burning or a dull ache (fig. 4*F*). These symptoms were associated with the involvement of the second or third cervical vertebrae, or both.

Back of the Neck.—Pain, aching, soreness and stiffness up and down the back of the neck from the cervical prominence (less frequently between the upper part of the shoulder blades) up to the occiput were the outstanding symptoms of this region. The sensation of a lump over the cervical prominence and, less frequently, of paresthesias, such as numbness, burning and tightness, were also symptoms (fig. 4*C*). These were associated with the involvement of the fifth and sixth or seventh cervical vertebrae.

Shoulders.—In this region, the symptoms consisted of pain, or aching, and soreness on the outer side of the neck. Radiation occurred outward over the shoulders and was described as "painful shoulders," or to the front of the chest as far down as the second interspace (excluding the space on the neck between the bellies of the sternomastoid) (fig. 4*D*). Stiffness of the shoulders was less frequently a symptom. Occasionally, there was a complaint of paresthesia, such as burning and tightness. When arthritis of the shoulder was present concomitantly with cervical arthritis, crackling in the shoulder joint was an added symptom. When symptoms over the back of the neck and the shoulder areas coexisted, radiation occurred from the side of the neck and shoulder to the outer side of the arm, and often to the base of the thumb (fig. 4*E*). These symptoms were described as pain, aching or heaviness. The osteo-arthritic process was found in the fourth, fifth and sixth or seventh cervical vertebrae, or the fifth and sixth cervical vertebrae alone, when the upper and posterior border of the fifth vertebra also showed arthritic changes.

Upper Part of the Chest (Precordium, Mammary Region).—Pain and aching over the precordium (second to fourth or fifth interspace) were outstanding symptoms. Pain, when acute, was sharp (like pins), and between acute episodes it was described as dull or aching. Radiation occurred to the armpit and down the inner side of the arm, often to the fingertips (fig. 4*I*). When symptoms were most pronounced on the left

side the patient frequently associated them with the heart, and, in certain introspective persons, tachycardia and fear of breathing would follow. Less frequently, symptoms of soreness and paresthesias, such as numbness and burning, were described. These symptoms were associated with the involvement of the upper four or five dorsal vertebrae.

Upper Part of the Chest (Between the Shoulders).—Soreness between the shoulders was practically the only complaint in this region, and existed usually as an extension of symptoms from the area up and down the back of the neck, or in conjunction with symptoms across the upper part of the chest, when the upper dorsal vertebrae were involved (figs. 4*I* and 5).

Lower Part of the Chest (Hypochondrium).—In the hypochondrium the symptoms were pain or aching with radiation to either side, along the costal margin to the shoulder blade, or heaviness, stabbing pain, pressure and "gas" across the epigastrium. Such symptoms on the right side were over the area of distribution of the referred pain of disease of the gallbladder (fig. 4*G*).

Epigastrium.—Pain and paresthesias, such as burning, tingling and heaviness, pressure, stabbing pain and "gas," were the symptoms in order of frequency. These extended bandlike across the epigastrium, or radiated across the hypochondrium, on either side, along the costal margin to the shoulder blade, as previously described, or as a girdle pain and aching across the navel. The latter would be referred to the upper part of the small of the back, just below the angles of the scapulae (fig. 4*G*). Symptoms in these areas were associated with the involvement of the middorsal vertebrae.

Lower Part of the Abdomen.—Pain, aching and stabbing were the main symptoms (the latter symptom usually occurred in the right lower quadrant), and, less frequently, soreness and burning. These were usually referred to the small of the back, or began posteriorly, and were referred from the small of the back where stiffness and weakness were occasional symptoms (fig. 4*H*). They were associated with the involvement of the three lower dorsal vertebrae.

Inguinal Ligament, Side of the Thigh and Upper Front Part of the Thigh.—Pain, burning or aching, starting over the upper outer aspect of the thigh, at or behind the crests of the ilium, were the main symptoms of the patient's chief complaint. Radiation occurred into the area over the inguinal ligament, or across the front of the thigh to the inner aspect and downward to the knee and, less frequently, to the inner side of the leg. Questioning was often necessary to determine the distribution of the radiation. Tenderness to pressure, below the lateral part of Poupart's ligament, was occasionally present (fig. 4*J*). Symp-

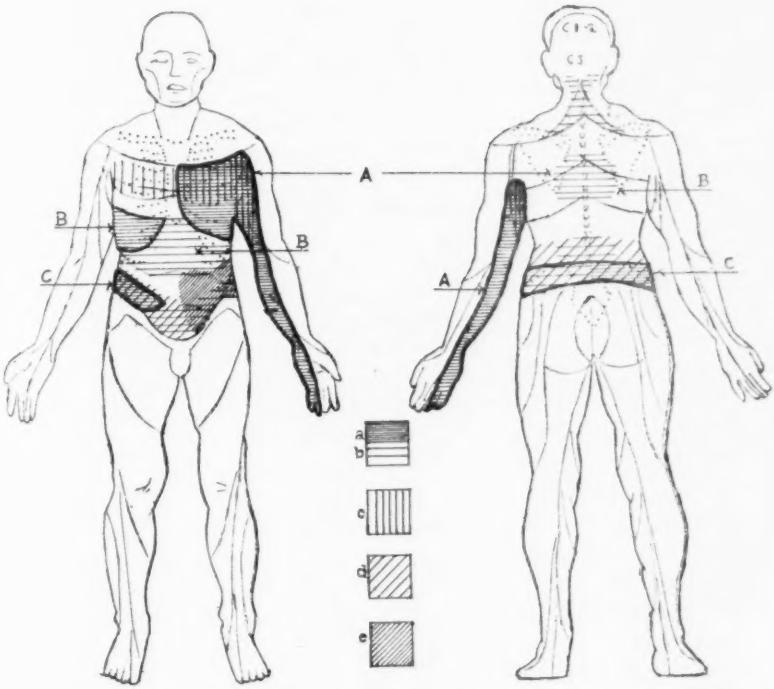

Fig. 5 (case 5).—Illustrating pseudo-angina pectoris, pseudo-appendicitis, gastric disturbances and pseudocholecystitis. *A*, the radicular distribution of the dorsal roots 1, 2, 3, 4, 5 and 6; subjective sensory disturbances for a period of twelve years, acutely for five months; disturbances worse on the left; mistaken diagnosis of angina pectoris. *B*, the radicular distribution of the dorsal roots 6, 7, 8 and 9; subjective sensory disturbances over a period of twelve years, worse on the right; associated with the "stomach" by the patient; diagnosis of chronic cholecystitis and investigation for disease of the gallbladder was made. *C*, the radicular distribution of the dorsal roots 10, 11 and 12; subjective sensory disturbances for several years; symptoms greatest on the right; a diagnosis of chronic appendicitis was made; the surgeon advised appendectomy; area of backache over the "small of the back." *a*, subjective sensory disturbances; area of chief complaint; *b*, subjective sensory disturbances; other areas brought out in the past history; *c*, moderate increase in sensation to the cotton tuft; *d*, moderate decrease in sensation to the cotton tuft; *e*, marked decrease in sensation to the cotton tuft.

toms in this area were associated with the involvement of the upper lumbar vertebrae above the third lumbar vertebra.

Symptoms on the inner side of the leg were more often associated with symptoms of localized pain over the sacrum (fig. 4*B*). The latter pain will be explained fully later.

Over the Sacrum.—Pain was the outstanding symptom in this area. As a symptom, localized pain over the sacrum (backache) was often present along with pain on the inner side of the leg. The patient spoke of backache, but closer scrutiny revealed a localization to the area over the sacrum. Most frequently, the pain radiated down the posterior middle part of the thigh to the popliteal space (the peripheral distribution of the posterior cutaneous nerve of the thigh), thence to the outer side of the leg to the dorsum of the foot (the peripheral distribution of the external popliteal nerve) (fig. 4*A*). Paresthesias, such as numbness and tingling over the posterior surface of the thigh and over the dorsum of the foot, were less frequent symptoms. Sciatic pain was associated with the involvement of any of the following: the third lumbar vertebra, the lumbar vertebrae below it, a sacralized transverse process of the fifth lumbar or arthritic changes about the sacro-iliac joint.

GENERAL SYMPTOMATOLOGY; FACTORS WHICH INDUCED OR AGGRAVATED SYMPTOMS

The cardinal symptoms were pain, aching and soreness, brought on or aggravated by the movement of the spinal column. The most common factors that induced or aggravated the symptoms were sneezing, straining at stool, coughing (Dejerine's sign), rising after a sitting position, raising the head on awakening, getting out of bed, walking, sitting in one place for any length of time, a change of position and lifting. Pain at night, which awakened the patient and was relieved by a change of position was commonly noted. Inability to sit up in bed from a supine position, without producing pain, and the necessity of rolling out on one side or the other were quite characteristic. Many of the patients preferred a hard bed, obtaining most rest when lying flat on the back. The wearing of a corset, strapping, heat and massage were measures that gave relief.

Pain, induced or aggravated by movement of the spine, as described before, in some form or other, was common to all cases. Dejerine's sign (coughing, sneezing and straining at stool) occurred first as the single factor which aggravated the symptoms in all the regions of the spine. The presence of this sign is useful but does not indicate the cause.[22] The acts, which constitute Dejerine's sign, outstandingly affected the back of the neck and shoulder regions, the area over the sacrum and the so-called sciatic distribution. In the neck, sneez-

ing induced symptoms oftener than coughing or straining; and over the small of the back and sacral regions, straining at stool was more often an aggravating factor. It is noteworthy that sneezing affected the upper spinal roots more than straining at stool, and the latter, in turn, affected the lower spinal roots. This may be explained by the mechanics of the acts involved. The acts that constitute Dejerine's sign cause an increase in intraspinal pressure and probably act mechanically on the roots and the meninges of the roots. The latter have already lost their elasticity incidental to sequellae of the osteo-arthritic process.[29]

Coughing is the least aggravating factor of the three that constitute Dejerine's sign. In the absence of pulmonary infection, coughing is ordinarily done lightly, as in clearing the throat. No doubt, if coughing were indulged in severely enough to raise the intraspinal pressure to the same degree as occasioned by sneezing and straining at stool, symptoms might be induced and aggravated to as great a degree. All regions were particularly affected by any position that induced relaxation of the protecting muscles, such as lying in bed and prolonged sitting in one position.

Pain, as seen in this study, was a bothersome symptom and sometimes troublesome enough to interfere with work. It was not, as a rule, severe and not in any instance was it extreme enough to require opiates. It lacked the severity of the pain seen in Pott's disease and in tumors of the vertebrae and cord. The spontaniety seen in the latter condition was not present. Movement, or the Dejerine sign, was always the provoking factor. Localized vertebral pain and tenderness, as seen in Pott's disease and new growths of the vertebrae or cord, were not present. While pain was a symptom which appeared at night and interrupted the patient's sleep, in no case did the patient walk the floor or sleep in a chair for relief. This symptom appears in new growths of the cord and vertebrae, and has been stressed by Parker and Adson.[12] In fact, in our patients such maneuvers invariably aggravated symptoms.

SENSORY ALTERATIONS

For the most part, the sensory changes were bilateral in distribution. The most common observations were hyperesthesia, hypesthesia or anesthesia to the cotton tuft. When hypesthesia to the cotton tuft was marked, a slightly decreased sensibility to the pinpoint was also found to be present. In a given patient, altered responses to heat and cold were in the same direction as those elicited with the cotton tuft or the pin.

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29. Bechterew (footnote 1). Bailey and Casamajor (footnote 11). Nathan (footnote 18).

Hyperesthesia to the cotton tuft was commonly found in patients with complaints dating within one year. Occasionally, a patient with symptoms of many years' duration suffered an acute attack in a given region. Hyperesthesia was found when the exacerbation of symptoms was of less than one year's duration. In the areas supplied by the lower cervical roots, and the lower lumbar and upper sacral roots, hyperesthesia was occasionally found in patients with symptoms of five or more years' duration. Hypesthesia to the cotton tuft was common in patients whose symptoms extended beyond a period of five years, and occasionally could be found in cases in which the symptoms were of less than three or four years' duration. Marked hypesthesia to the cotton tuft, anesthesia to the cotton tuft and slight hypesthesia to the pin stroke were generally found in patients with symptoms of more than five years' duration, and rarely in patients with symptoms of between three and five years' duration.[30]

Sensory disturbances varied in extent, severity and character, from a small area of hyperesthesia to a sensorium dulled to light touch over most of the body. Such alterations in the sensation of light touch were found constantly, and it became possible, after a number of examinations, to chart out the entire body and to anticipate from the chart the levels of the spinal vertebrae at which pathologic processes might occur.

X-Ray Changes.—In the well marked hypertrophic process, the presence of spurs on the anterior and lateral parts of the bodies of the vertebrae requires little comment. Hypertrophic spurs were also noted on the posterior margins of the vertebrae. Fluffiness and fuzzy projections were noted along the margin of the bodies in certain cases, which we believe indicate the earlier x-ray changes of hypertrophic spinal osteoarthritis. Loss of the intervertebral disk substance was noted particularly in those patients who showed abnormal bowing of the spinal column, and was seen especially in the dorsal vertebrae. In the extremely marked process, a certain degree of atrophy of the bodies of the vertebrae was noted. Calcification of the anterior ligaments that appeared as though molten bone had been poured over several of the vertebral bodies, without apparent loss of intervertebral disk substance, was seen in two patients who elsewhere in the spine showed the more common spur formations. The varied changes observed were associated with nerve root symptoms and alterations of sensation at the particular vertebral level that was involved.

30. In patients studied since this series was analyzed, the A and B pinching tests of Carnett (Carnett, J. B.: Intercostal Neuralgia as the Cause of Abdominal Pain and Tenderness, Surg. Gynec. Obst. **42**:625 [May] 1926) were found useful when marked hyperesthesia and hyperalgesia were present over the abdomen.

BLOOD PRESSURE

Hypertension was not a prominent observation in this study. In twenty-four patients, the readings for the systolic blood pressure varied between 100 and 150. In five patients, the readings for the systolic blood pressure varied between 154 and 162. One patient had a systolic blood pressure of 184.

In twenty-six patients, the readings for the diastolic blood pressure varied between 66 and 80. For the remaining four patients of the series, two diastolic readings were obtained at 98 and 102 and two at 120 and 124.

RÉSUMÉ

As may be seen from the foregoing facts, the symptomatology may be diffuse, depending on the vertebral levels involved. Cervical involvement is associated with headache, sore neck, painful shoulders and arms. Upper dorsal involvement is associated with precordial pain, which is considered by the patient, and often by his physician, to be of cardiac origin. Pain in the epigastrium and over the region of the gallbladder was noted when the mid-dorsal vertebrae were involved. Pain over the lower part of the abdomen, which required a differential diagnosis from appendicitis and pelvic disease, was associated with the involvement of the lower dorsal vertebrae. Involvement of the lumbar vertebrae was associated with painful hips and thighs as in disease of the hip joint, and as in so-called meralgia paraesthetica, or with pain over the back and lower extremities, as in sciatica.

It becomes apparent from the widespread nature of the patient's complaints that involvement of various spinal roots may be associated with subjective sensory disturbances, seemingly due to visceral disease, and herein lies the importance of recognizing the radicular syndrome based on spinal osteo-arthritis.

REGIONAL RADICULITIS: CERVICAL RADICULITIS

Since arthritis of the spine as a cause of the radicular syndrome has received little attention, it is not at all surprising that root pain corresponding to the distribution of the first to third cervical roots over the head has been commonly included under the blanket term of "headache." These roots supply the back of the head from the occiput to the vertex and a small area over the mandible (figs. 3 and 4*F*).

Headache.—Irritation of the first three cervical roots manifests itself subjectively to the patient as "headache" over the occiput, the back of the head and the vertex. This type of headache has been commonly spoken of in the literature as "indurative or rheumatic head-

ache," and has been thought to be due to fibrositis or fibromyositis of the fascia, which these nerves pierce in order to gain the periphery.[31]

Hartenberg [32] commented on the association of indurative headache and arthritis of the cervical spine. Indurative or rheumatic headache has so many striking points of similiarity with arthritis that Patrick [33] labeled it "arthritic headache." Holmes [31] showed that a pathologic process in the higher cervical vertebrae could be the cause of persistent headache, and ascribed it to irritation of the spinal roots that furnish fibers to the occipital nerves. In his case, tuberculosis of the first cervical vertebra was considered the causative agent of irritation of the roots.

Patrick, in discussing indurative or rheumatic headache, gave an interesting review of the discovery, by Scandanavian masseurs, of tender nodules occurring in occipital, suboccipital and vertex headache. He pointed out the inaccuracy of palpation of the nodules by masseurs and others, whose anatomic and physiologic knowledge was not accurate, "Nodules can be felt by anyone—and a masseur is especially apt to be feeling things—especially glands, subcutaneous fat, etc." Patrick did not believe that palpable nodules had any connection with the disease. He cited Auerbach, who found a nodule the size of a nut in one patient who presented symptoms, and a similar "kernal" in another patient without symptoms, and in conclusion pointed out the necessity for further investigation of localized lumps by "real pathologists, rather than by masseurs." In discussing indurative headache, Holmes [31] cited Muller, who insisted that the palpable nodules were not the essential factors of the headache, but that they were due to the higher tonus of the affected muscle, which, on the other hand, was a result of latent arthritis in the adjacent joints. When a careful analysis of Patrick's description of indurative headache is made, the radicular distribution of the radiation of pain and the factors common to cervical radiculitis become striking. Symptoms, he stated, are brought on by stooping, straining, coughing and, generally, physical exertion.

In 1927, Holbrook [34] described a series of cases in which headache was the prevailing symptom. Hypertrophic osteo-arthritis of the upper cervical vertebrae was a constant observation.

In this series of thirty cases, eight patients complained of headache. This group presented certain common symptoms, which were characteristic enough to enable one to recognize the syndrome quite

31. Holmes, Gordon: Headaches of Organic Origin, Practioner **90**:968, 1913.
32. Hartenberg, M., quoted by Patrick (footnote 33).
33. Patrick, H. T.: Indurative or Rheumatic Headache, J. A. M. A. **71**:82 (July 13) 1918.
34. Holbrook, C. S.: Headache Due to Arthritis of the Cervical Spine, South. M. J. **20**:225 (March) 1927.

readily. These were pain dependent on movement of the neck, or on relaxation of the supporting structures of the cervical spine, as in sleep, and aggravation or induction of symptoms by Dejerine's sign (coughing, straining and sneezing).

Headache was described as a dull ache, or soreness and burning at the occiput on either side, or both sides, which "shot" most commonly to the vertex, and less frequently radiated from the occiput to the side of the head and temples. Headache was a symptom when the second or third cervical vertebrae, or both, were involved. In order of frequency, subjective sensations at the vertex were piercing pain, tenderness, soreness, burning or dull aching.

Symptoms were uniformly produced or aggravated by movement of the head. According to frequency, Dejerine's sign, sudden movement and raising the head on awakening were the most common aggravating factors. The patient awakened at night with this pain and found relief by a change of position. As previously pointed out, a hard bed was preferred, the patient obtaining greatest relief when lying flat on the back. The wearing of a splinting collar, heat, massage and stretching of the neck were measures which gave relief. On movement, audible crepitations in the neck were frequently noticed. Occasionally, tenderness at the occiput was observed. The symptoms tended to disappear after the patient had been up and around after rising, provided he did not move the neck suddenly.

The patient complained of "headache," without the likelihood that actual headache existed. The presenting symptomatology was that of pain and aching over the distribution of the first, second and third cervical roots over the back of the head, and was always found when the second or third cervical vertebra, or both, showed an osteo-arthritic process. Headache was not a solitary symptom, but was found in association with symptoms over the area "up and down the back of the neck." Symptoms over this area were associated with osteo-arthritis involving the fifth and sixth or seventh cervical vertebrae. Headache, per se, as a symptom was not present in patients who showed a localized lower cervical osteo-arthritis, unless the upper cervical vertebrae also showed evidence of pathologic changes.

Involvement of the cervical roots with symptoms of headache may also occur in other pathologic processes of the higher cervical vertebrae, as pointed out by Holmes.[35]

35. Holmes (footnote 31). Worthy of mention is one patient not included in this series, who presented symptoms over the distribution of the first, second and third cervical roots following an ankylosing process which involved the upper three cervical vertebrae. The x-ray picture interpreted by the roentgenologist read: "An old destructive process probably the result of an infectious arthritis."

Sore Neck and Painful Shoulders and Arms.—Discussions on spinal osteo-arthritis associated with cervical radiculitis have been reported chiefly in the French literature [36] as rheumatic diseases of the spine and as rheumatic radiculitis. In the older English literature, frequent references were made to the occurrence of brachial neuralgia and neuritis in "rheumatic and gouty people." [37] Buckley [38] stated that, "apart from injury, gout is undoubtedly the most prominent etiological factor and in many cases the only discoverable cause, while in others it acts merely as a predisposing condition." Rheumatism and gout were apparently used by the earlier French and English writers in a general manner, indicating the group of deforming arthritic diseases, rather than being restricted solely to the disease associated with disturbances in uric acid metabolism.

Buckley also observed sensory alterations such as anesthesia and hyperesthesia. These changes were very slight, but often were present after other symptoms had disappeared. Other reports can be found, such as Distin's,[39] in which the clinical description strongly suggested the presence of spinal osteo-arthritis and associated involvement of the spinal roots. In this country, Bassoe,[20] Elliott [28] and Nielsen [40] associated cervical osteo-arthritis with radicular symptoms in neuritis of the shoulders.

Symptoms referable to the lower cervical roots were found in eighteen patients in this series. Thirteen of these described symptoms "up and down the back of the neck" and the side of the neck, with radiation over the shoulders and the outer side of the arms. One patient of this group complained of pain at the side and front of the neck; a diagnosis was made of adenomatous goiter with thyrotoxicosis, and the patient was referred to the University of California Hospital for thyroidectomy. Observation on the surgical service failed to confirm the diagnosis, and the patient was referred to the outpatient department for further study. Five patients complained solely of symptoms "up and down the back of the neck." Painful shoulders (fig. 4*D*), or aching and soreness on the outer side of the neck, and pain, aching, soreness and stiffness "up and down the back of the neck" (fig. 4*C*) were complained of when the fourth, fifth and sixth or seventh cervical vertebrae were involved. Pain radiating down the outer side of the arms, often to the base of the thumbs, was part of the picture, and occasionally paresthesia in the fingers in the form of tingling and numbness was

36. Camus (footnote 4). Leri (footnote 5).
37. Simon, R. M.: Brachial Neuralgia, Brit. M. J. **2**:71 (July 11) 1903.
38. Buckley, C. W.: Brachial Neuritis, Lancet **1**:1042, 1904.
39. Distin, H.: A Note on Brachial Neuralgia, Brit. M. J. **1**:124, 1904.
40. Nielsen, J. M.: Radicular Syndrome, J. A. M. A. **88**:1623 (May 21) 1927.

present. Over the outer side of the arm, the symptoms were described as pain, aching or heaviness. When the fifth and sixth, or fifth to seventh cervical vertebrae alone were involved, the subjective complaints were often restricted to the area "up and down the back of the neck," between the cervical prominence and the occiput (fig. 4*C*). If the shoulder, or the acromioclavicular joint, was also the seat of arthritic changes, crepitation in the shoulder was an added symptom.

The cardinal symptoms were pain, aching and soreness, induced or aggravated by movement of the spinal vertebrae, associated most commonly with sneezing, straining at stool and coughing (Dejerine's sign) and raising the head on awakening. Sneezing induced symptoms more often in the cervical spine than coughing or straining at the stool. Other aggravating factors and symptoms have been described in detail, in the section on general symptomatology.

Sensory tests with the cotton tuft, as previously outlined, were conducted on all patients of this group. Sensory changes were, for the most part, bilateral in distribution. Hyperesthesia could be found more often in the cervical region, in patients with symptoms of more than five years' duration, whereas, in other regions, hypesthesia was common. Anesthesia to the cotton tuft was noted in the cervical region, when the symptoms were of more than five years' duration, but did not occur as frequently as elsewhere. Flattening of the thenar and hypothenar eminences was noted in certain patients, but actual paralysis of these muscle groups could not be demonstrated.

Physical examination usually showed restricted mobility of the cervical spine. Motion induced crepitations over the back of the neck, which could be heard with the stethescope, and sometimes these were palpable. When arthritis of the shoulder joint was also present, crepitations could be elicited on movement of the shoulder joint.

To the laity, the condition of painful shoulders is commonly known as neuritis, neuralgia and sore arms. Because the pain is referred to this area, the shoulder joint receives considerable undeserved attention. Even the thyroid is not immune from suspicion when pain is referred to the side and front of the neck. Arthritis of the shoulder joint and osteo-arthrititis of the cervical spine may exist together. Errors in diagnosis can be avoided only by a careful study of each case, taking into consideration the nature and distribution of the symptoms, and the careful examination of the shoulder joint, as suggested by Patrick.[33] Sensory alterations, of the nature described, cannot be explained by disease of the shoulder joint. Involvement of the anterior cervical roots, resulting in confusion with the muscular atrophies of the upper extremity and shoulder girdle, has been reported.[40]

DORSAL RADICULITIS

Heart Disease, Heart Neurosis, Pulmonary and Pleural Disease and Operations on the Breast.—In a paper on the importance of examination of the spine in the presence of thoracic and abdominal pain, Phillips [41] called attention to pain over the precordium simulating angina pectoris. He did not test for sensory disturbances. Kilgore,[42] reporting a large series of cases with precordial pain, noted that in the normal group a common type of precordial pain was related to certain movements of the left arm, position in bed, etc. To the normal group, he applied the term "psuedo angina pectoris." Although he did not ascribe the syndrome to spinal osteo-arthritis, he pointed out the character of the pain, which was different from that of true angina.

Heart disease occupies the attention of the patient when the second to the fifth dorsal vertebrae are involved, and the physician is apt to be misled by complaints of pain and aching over the precordium with radiation in an anginoid manner toward the shoulder and the armpits, down the inner side of the arm and often to the small finger (fig. 4*I*). To a certain extent, in introspective persons, tachycardia and fear of breathing are concomitant sensations. Soreness and paresthesia, such as numbness and burning, are also symptoms. The physician recognizes the exaggerated apprehension of the patient, and the picture of the neurotic or the irritable heart, or, if the attack is severe, of angina pectoris is simulated.

Unlike the condition in patients with angina pectoris, however, the blood pressure of these patients is either within normal limits, or other outstanding evidences of vascular disease are absent. They get little relief from the usual symptomatic treatment, their complaints are persistent, they see many physicians and it is not unusual to find that they have been labeled as "neurotics," or classed under other "waste basket" terms. While the pain may radiate as in angina pectoris, the outstanding feature of this syndrome is the aggravation or onset of symptoms with movements of the spine, even when the patient is at rest, such as being awakened at night by pain, or onset of pain when sitting in a chair. The nocturnal pains are relieved by a change of position. The symptoms described in the paragraph on general symptomatology apply to this group also.

When the symptoms in the upper part of the chest are most severe on the right side and Dejerine's sign to coughing and sneezing is

41. Phillips, John: The Importance of Examination of the Spine in the Presence of Intrathoracic or Abdominal Pain, Proc. Interstate Post Graduate Medical Association of North America, Kansas City **3**:79 (Oct. 17-21) 1927.

42. Kilgore, E. S.: Angina Pectoris and Pseudo-Angina: A Clinical Study with Especial Reference to Lancinating Pain, J. A. M. A. **87**:455 (Aug. 14) 1926.

positive, the condition may be diagnosed as tuberculosis or pleurisy. If the patient is a woman in the cancer age, she and the physician focus considerable attention on the breasts, and operation for the removal of a "pea-sized" benign cyst may be the result.

Symptoms over the distribution of the upper five dorsal roots were found in ten patients. Of these, tuberculosis with pleurisy had been diagnosed in one, and pleurisy of the left side in another. In the former patient, at the time of onset, Dejerine's sign was positive to coughing and sneezing. The symptoms were greatest on the right and were confined to the area supplied by the second to fifth dorsal roots. These circumstances led to a diagnosis of tuberculosis with pleurisy. In the history, sufficient weight was not given to the fact that the pain was radicular in distribution, and movements of the spinal column, such as stooping and getting in and out of bed, were as prominent in the induction of symptoms as were coughing and sneezing. The laboratory work, necessary to confirm a diagnosis which was to alter this patient's mode of living, was not obtained. Four patients, including the one whose condition was diagnosed pleurisy of the left side, complained of heart trouble and were examined for cardiac disturbances (fig. 5). Three had symptoms across the upper part of the back, between the shoulder blades. Two patients, who did not have complaints referred to this area, were found to have suffered from disturbances over the upper part of the chest and back in previous years. One of the latter patients has been included in those who complained of heart trouble. One patient in the cancer age had a benign cyst, the size of a pea, removed from the left breast. The surgeon remarked that the amount of pain and disability was not accounted for by the cyst. The same patient, at another examination, was said to be neurotic, because of the diffuseness of her symptoms.

Gastric Disturbances and Diseases of the Gallbladder.—Osteo-arthritic involvement of the sixth, seventh, eighth and ninth dorsal vertebrae was associated with pain, burning, tingling, heaviness, pressure and stabbing, and "gas" in the epigastrium, and the patient associated these symptoms with the digestive apparatus. For such conditions, it was not uncommon for patients to have consulted gastro-enterologists.

Involvement of the same roots, with manifestations greater on the right side, was revealed as pain or aching over the right upper quadrant with radiation along the ribs to the shoulder blade, or across the abdomen. This area, the topographic distribution of dorsal roots six to nine, is the same area over which pain from a diseased gallbladder is referred (fig. 4*G*). Pain in this region must be differentiated from disease of the gallbladder. Osteo-arthritis of the spine with root pain may account, perhaps, for the large percentage of operations on the gallbladder that

fail to give relief. Muller,[43] in a discussion of the noncalculus gallbladder, pointed out that from 30 to 40 per cent of patients still complain of symptoms after operation, and he urged against the diagnosis of disease of the gallbladder on threshhold symptoms, and against operation in the absence of gross demonstrable lesions, as shown by cholecystography and other methods. The observations in this series indicate the necessity of a careful analysis of each case, and the presence of osteo-arthritis of the spine should be given due consideration in the absence of outstanding symptoms of disease of the gallbladder. Carnett,[44] in a discussion of the disease of the gallbladder simulated by intercostal neuralgia of the abdominal wall, also discussed the problem of the unsatisfactory end-results of operation on the gallbladder without calculus.

Disease of the gallbladder and radicular symptoms in spinal osteoarthritis may coexist. The train of symptoms produced by each can be separated quite readily.

Fourteen patients presented symptoms over the distribution of the sixth to ninth dorsal roots; six patients complained of stomach trouble and pain in the left hypochondrium. Three of these had first visited gastro-enterologists. One history of the three disclosed a long list of therapeutic procedures, including surgery and a Sippy diet, all of which had been tried without success. Both the patient and the physician considered the symptomatology of gastro-intestinal origin. The history did not show any clearcut indication for the Sippy regimen, and our examination and laboratory procedures likewise directed attention away from the gastro-intestinal tract. Interestingly, another physician had prescribed an orthopedic belt for the patient, and it also had failed to furnish relief. Examination of the belt showed it to be of the "low-back" variety, designed for support of the lumbar spine. It was not long enough to furnish any sort of support to the mid-dorsal spine where support was most needed. This mistake indicates the necessity of the physician having a working knowledge of the distribution of nerve roots. To be effective, a belt for relief of radicular pain of the lumbar region should be large enough to support the mid-dorsal and lower dorsal regions of the spine.

Four patients presented symptoms over the distribution of referred pain of the gallbladder, and three were originally studied for disease of the gallbladder. One history of the three showed entries in the cardiac clinic for angina pectoris (precordial pain), in the gastro-intestinal

43. Muller, G. P.: The Noncalculus Gallbladder, J. A. M. A. **89**:786 (Sept. 3) 1927.

44. Carnett, J. B.: The Simulation of Gallbladder Disease by Intercostal Neuralgia of the Abdominal Wall, Ann. Surg. **86**:747 (Nov.) 1927.

clinic for chronic cholecystitis (pain in the right upper quadrant) and in the surgical clinic for chronic appendicits (pain in the right lower quadrant). The symptoms varied only in their location (fig. 5). The fourth patient had a chronic fibrous cholecystitis, without stone, and radicular symptoms coexisting. Cholecystectomy failed to relieve the outstanding symptom, pain. Another patient, in whom exploratory laparotomy revealed a carcinoma of the gallbladder, presented symptoms of chronic cholecystitis, which were partially masked by the symptoms of an upper dorsal radiculitis with pain over the precordium and a mid-dorsal radiculitis with involvement of the same roots over which pain is referred from the gallbladder. Sensory alterations, consisting of hypesthesia to the cotton tuft were present. One case was diagnosed as pleurisy, of the right side, and one patient in addition complained of radicular headache. The past history of one patient who did not have any complaints referable to the mid-dorsal roots revealed an area of root distribution that had previously been troublesome.

Pseudo-Appendicitis.—Discussions of extra-abdominal lesions as the cause of a syndrome simulating appendicitis have been presented by Carnett,[45] a surgeon, and by Phillips,[41] an internist. The former reviewed the literature of so-called psuedo-appendicitis, and ascribed the condition to intercostal neuralgia of the lower intercostal nerves. He discussed the methods of differentiating this condition from acute and chronic appendicitis.

Phillips called attention particularly to the osteo-arthritic spine as a cause of irritation of the lower dorsal roots. Symptoms were manifested peripherally as pain over the lower part of the abdomen, and included the region of the appendix.

Reference to figure 3 shows that the tenth to twelfth dorsal roots supply the area over the lower part of the abdomen between the umbilicus and inguinal ligaments, and posteriorly between a line drawn through the twelfth dorsal spine, above and the iliac crests, below. In this series, it was found that when the tenth to twelfth dorsal roots were affected, the appendix received considerable attention when the symptoms were greatest on the right; in women, the tubes and adnexa preceived attention when the symptoms were greatest on the left. Pain aching and stabbing (the latter usually in the right lower quadrant), which was referred to the small of the back, or began there and radiated forward across the abdomen, were the commonest complaints and were associated with osteoarthritic involvement of the tenth to twelfth dorsal vertebrae. As shown in the section on general symptomatology, symp-

45. Carnett, J. B.: Chronic Pseudo-Appendicitis Due to Intercostal Neualgia, Am. J. M. Sc. **174**:579 (Nov.) 1927; Acute and Recurrent Pseudo-Appendicitis Due to Intercostal Neuralgia, Ibid. **174**:883 (Dec.) 1927.

toms were induced by movement, as in walking, stooping and bending, and were associated with coughing, sneezing and straining, or came on at night when the patient slept. Relief was obtained by mechanical means, such as strapping the back. Sensory changes in this area were similar to those found in other regions.

Fifteen patients in this series had symptoms over the distribution of the tenth to twelfth dorsal roots, associated with osteo-arthritis of the adjacent vertebrae. Four of these complained chiefly of disturbances in the right lower quadrant, two had been operated on for appendicitis without relief of symptoms and a third had been urged to submit to an appendectomy (fig. 5). The last patient still has her appendix. One of the two patients who had been operated on for chronic appendicitis showed an isolated osteo-arthritic involvement of the ninth, tenth and eleventh dorsal vertebrae. The outstanding symptom in the post-appendectomy cases and in the patient who refused to submit to the operation, was pain dependent on movement of the spine, or associated with coughing, straining and sneezing. The presence or absence of the appendix has not altered the situation at all, for each continued to suffer from pain. Four of eleven who complained of pain across the lower part of the abdomen, also complained of backache across the small of the back. Two had undergone operations on the pelvis organs, without relief of symptoms.

If the existence of pain referred from a distant point with origin in the spine is kept in mind in the differential diagnosis in conditions of the lower part of the abdomen, particularly in patients over the age of 35, the diagnosis of appendicitis based on minimal symptoms will not be made in the absence of the order of occurrence of symptoms, as stressed so strongly by the late John B. Murphy.[46] A history, carefully elicited, will bring out the relation of pain to movement, and to coughing, sneezing and straining, and other root areas not complained of at the time will be uncovered.

LUMBAR RADICULITIS

Meralgia Paresthetica and Arthritis of the Hip Joint.—Pain, burning or aching, starting over the upper part of the thigh at or behind the iliac crests, at the sides of the thigh with radiation into the inguinal ligament area or downward across the front of the thigh to the knee (fig. 4*J*), were complained of by six patients who showed an osteo-arthritic process localized to the upper lumbar vertebrae. Rosenheck [14] and Bassoe [20] considered osteo-arthritis in this region of the spine a cause of so-called

46. Murphy, J. B., quoted by Cope in The Early Diagnosis of the Acute Abdomen, ed. 4, London, Oxford Medical Publications, 1927, p. 62.

meralgia paresthetica. Stookey [47] did not consider Rosenheck's cases as true meralgia paraesthetica, because of the radicular nature of their disturbances. When symptoms are confined to the upper part of the thigh, the pain, as in the region of the shoulder, is often ascribed to arthritis of the adjacent joint. In this series, the fabere [48] sign, as suggested by Patrick,[33] was noted. Cases were not included in this group unless the symptoms and sensory changes were purely radicular in distribution.

REPORT OF CASE

P. A., a housewife, aged 40, had suffered at various times during the past ten years from pain up and down the spine; pain, soreness or burning, which radiated from the small of the back to the lower part of the abdomen; pain up and down the back of the neck, and occipital "headache" which sometimes radiated to the top of the head. Movement, such as getting in and out of bed, induced or aggravated symptoms. Fourteen months before examination an appendectomy was performed, because of the pain in the lower part of the abdomen. The symptoms were not relieved.

The symptoms of her present illness were pain, soreness and burning, beginning at the iliac crests, more severe on the right and radiating down the outer side of the thigh over the distribution of the lateral femoral cutaneous nerve of the thigh. On questioning, it was found that radiation also extended across the front and the inner side of the thigh to the knee. The total area of subjective disturbances covered the distribution of the first to the third lumbar roots (fig. 4 *J*), which was made up of four peripheral nerves: the lateral femoral cutaneous, the anterior femoral cutaneous, the lumbo-inguinal and the ilio-inguinal nerves of the thigh. Symptoms were worse during the night, and were induced or increased by straining at stool, sitting in one position any length of time or attempting to rise from a chair.

Physical examination revealed two operative scars, one in the midline and one over the McBurney area. Marked tenderness to pressure was present below the anterior iliac spines. Examination of the back showed moderate restriction of mobility of the lower part of the dorsal spine. Sensory examination with the cotton tuft revealed hypesthesia over the back of the neck, and between the upper parts of the shoulder blades, corresponding to the fifth to the seventh cervical roots; hypesthesia over the small of the back between the twelfth dorsal spine and the sacrum, corresponding to the ninth to twelfth dorsal roots, and over the upper sides of the thigh, the front and inner sides corresponding to the first three lumbar roots. The fabere sign was not elicited. Gastro-intestinal consultation, including a gastro-intestinal series, genito-urinary consultation and cystoscopy and gynecologic consultation failed to uncover pathologic changes that would explain her symptoms. The consultants felt that the source of the trouble was outside the abdomen. The Wassermann reaction of the blood and the results of a Kahn test were negative. X-ray examination of the spine showed osteo-arthritic changes about the first, second, sixth and seventh cervical vertebrae, the sixth dorsal vertebra, the ninth to twelfth dorsal vertebrae and the first lumbar vertebra.

47. Stookey, Byron: Meralgia Paraesthetica: Etiology and Surgical Treatment, J. A. M. A. **90**:1705 (May 26) 1928.

48. The word "fabere" was introduced by Patrick to describe the movements of the thigh, in performing the maneouvers of this test, namely, flexion, abduction, external rotation and extension.

Comment.—In the history of the chief complaint, the patient presented symptoms of pain and paresthesias over the distribution of the lateral femoral cutaneous nerve of the thigh (old term, external cutaneous). Objective sensory disturbances were present in this area. Had the patient not been questioned regarding the total radiation of the subjective disturbances, the radicular nature of the symptoms would not have been clear. Confining oneself to the chief complaint, pain and paresthesias along the lateral aspect of the thigh, this case might have passed for one of meralgia paraesthetica. Disturbances in this patient, however, were bilateral (fig. 4*J*), and symptoms were dependent on movement of the spine and Dejerine's sign. While meralgia paraesthetica by definition is a syndrome affecting a peripheral nerve, namely, the external cutaneous nerve of the thigh, it is readily seen that the radicular nature of the osteo-arthritic syndrome affecting the roots of origin of this nerve might easily be overlooked. Rosenheck [14] particularly pointed out that the condition known by definition as meralgia paraesthetica has not been separated from the painful paresthesias of the thigh of radicular distribution, due to spinal osteo-arthritis.

Sciatica.—Localized pain over the sacrum and often present in conjunction with pain on the inner sides of the legs (fig. 4*B*), or pain over the sacrum radiating downward over the anatomic distribution of the first and second sacral spinal roots (fig. 4*A*), was found when an osteo-arthritic process was present anywhere below the level of the third lumbar vertebra. A similar condition and distribution also were found when a sacralized transverse process of the fifth lumbar vertebra or disease of the sacro-iliac joint was present. Distribution of pain over the first and second sacral roots is commonly called sciatica, and includes the cutaneous distribution of the posterior cutaneous nerve of the thigh and the peroneal division of the sciatic nerve. Paresthesia, such as numbness and tingling over the posterior surface of the thigh and over the dorsum of the foot, were occasionally symptoms.

The radicular nature of sciatica, with its subjective and objective sensory disturbances, has been recognized by orthopedists and has been amply described by Danforth and Wilson,[13] and by others. Our patients showed objective sensory alterations as tested with the cotton tuft and subjective disturbances dependent on motion, such as walking, bending and lifting and on straining, coughing and sneezing.

Symptoms over the roots, which are commonly involved in so-called sciatica, were present in twenty-three patients. Backache (localized pain over the sacrum) was the outstanding symptom. Sciatic radiation occurred in sixteen patients. Backache, concomitant with pain on the inner sides of the legs, was present in seven. One patient demonstrated sensory changes over the root distribution of sciatica at a time when

active symptoms were absent. Spinal osteo-arthritis coexisted with disease of the peripheral joints. The two conditions were also associated in four other patients. Symptoms were first noted thirty-five years before examination, and they were quiescent except in the region of the gallbladder. The history, however, was abundant in its information of the onset, progressive involvement of various spinal roots and session of symptoms in the various root areas during the many years. Bilateral sensory disturbances were demonstrable with the cotton tuft.

The most marked sensory disturbances of the entire series were found in a patient who complained of sciatica. Osteo-arthritic changes in the lower lumbar vertebrate and a left unilateral sacralized transverse process of the fifth lumbar vertebrae coexisted. Complete anesthesia to pain over the fifth lumbar and first sacral roots, and hypesthesia to the pin over the second sacral root was present on the same side.

Tender points along the sciatic nerve were not found. The Lasègue sign was inconstantly elicited and when present was extremely mild.

SUMMARY

Radiculitis may be defined as a symptom-complex manifested by alterations of sensation or of changed motor function, which show by their distribution that the disease is in the spinal root. The radicular syndrome in hypertrophic osteo-arthritis of the spine, as seen in this study, consisted of restricted mobility of the spine, root pains and root sensory alterations, produced or aggravated by movement, and associated with Dejerine's sign.

In the history of the chief complaint, it is commonly found that the patient outlines the cutaneous distribution of the root or roots involved with anatomic accuracy. In the past history, however, areas which were troublesome at some previous date, but were symptomless at the time, are not always outlined with the same degree of accuracy. The past history then becomes extremely important. If it is gone into carefully, previous symptom-bearing areas will be accurately outlined by the patient. In either event, it is important to determine the limits of each painful area and the extent of radiation of symptoms, because, in certain regions of the body, roots that are widely separated in the cord supply adjacent cutaneous areas. (The areas bordering the heavy lines in figure 3 should be noted.) If this procedure is adopted, the past history of even the apparently silent case will yield a story of chronological progression or regression and quiescence of the disease, and symptoms that indicate the involvement of various spinal nerve roots over a period of years. The charting of such cutaneous areas of nerve root distribution and a listing of the roots involved will enable one to anticipate the extent of the x-ray evidence of the osteo-arthritic process.

Pain at night, which awakens the patient and necessitates a change of position for relief, is a common symptom. Although the patient complains of one side more than the other, bilateral symptomatology is the rule, the right side receiving more attention over the abdomen, and the left side over the upper part of the chest and the precordium. Questioning is sometimes necessary to bring out the bilateral nature of symptoms. Characteristic of this syndrome is the root distribution of the symptoms. Measures which afford symptomatic relief are: lying flat on the back, or on a preferred side, a hard mattress, the placing of boards under the mattress, the wearing of a corset, or other mechanical means of immobilizing adequately the affected vertebrae, and physiotherapy, such as baking, heat and massage.

The outstanding symptom of this syndrome is pain. It is variously described, according to the patient's mode of expression. Symptoms are dependent on three factors: (1) movement of the spinal column; (2) relaxation of the supporting musculatures of the spinal vertebrae, and (3) mechanical factors which increase intraspinal pressure, such as coughing, sneezing and straining, as at the stool. These three acts are grouped together under the name of Dejerine's sign.

Under the heading of movement, typical phrases were encountered, such as rising after having been in a sitting position, raising the head on awakening, getting out of bed, walking, sitting in one place for any length of time, a change of position while sitting or lying, stooping, straightening after having been bent over, inability to sit up in bed from the supine position and the necessity of rolling out of bed on one side or the other. Under this category may also be included the reproduction of symptoms occurring during the various movements to which the spinal column is subjected when it is being tested for mobility. The mechanism involved under "relaxation of the supporting musculatures of the spinal vertebrae" explains the occurrence at night of symptoms which awaken the patient from sleep, the necessity of a change of position at night to obtain relief from pain, the preference for a hard bed and the relief obtained by placing boards under the mattress. The presence of the third factor, Dejerine's sign, is a useful sign in root-zone disease. This has been indicated by Dejerine[17] and by Mayer.[22] Dejerine's sign also occurs in other forms of disease of the spinal roots and does not give a clue to the etiologic factor. The presence of crackling in the neck, shoulders, hips or knees during movement, Heberden's nodes, and x-ray evidence of spinal osteo-arthritis, when associated with Dejerine's sign, furnish presumptive evidence of the osteo-arthritic etiology.

The sensory examination requires great care and patience. One or two areas were selected at a given examination, usually the area

of the chief complaint. Other areas were left for examination at another time. The selected area was tested once, the outlines of the involved area were recorded and no other sensory examination was made at that visit. This procedure was adopted because of the ease with which patients fatigue to the examination of light touch, and the confusion of results obtained when examination was continued after fatigue had set in.

Bilateral sensory changes were found, which consisted most commonly of hyperesthesia, hypesthesia or anesthesia to the cotton tuft. Marked hypesthesia or anesthesia with the cotton tuft was associated with slight hypesthesia to the pinpoint. Hyperesthesia to the cotton tuft was commonly present when the onset of symptoms dated within one year, or when an exacerbation of symptoms occurred in a given area within a year. Hypesthesia and anesthesia to the cotton tuft were common in patients whose symptoms extended beyond a five year period. In the area over the back of the neck, side of the neck and shoulders, the time relations were not so constant, hyperesthesia being more common than in other regions, even in patients with symptoms of many years' duration.

In patients with a long standing, diffuse, osteo-arthritic involvement of the spine, sensory changes were difficult to demonstrate, unless the hypesthesia was marked, or unless anesthesia to the cotton tuft was present. Such patients seemed to have a dulled sensorium to light touch over most of the body, and slight changes to light touch could not be demonstrated satisfactorily because of the lack of an unaffected area, other than the face, to use as a standard for comparison.

The physical examination revealed restricted mobility of the spine, varying from the involvement of a few vertebrae to the poker-like rigidity of the entire spine, which was seen in one patient. The vertebrae affected corresponded consistently to the origin of the roots involved, as determined in the history and in the sensory examination. The history and sensory examination, in turn, enabled one to anticipate accurately the pathologic process shown by the x-ray examination. Laboratory procedures, including the Wassermann test of the blood, gave normal values, or were negative. The results of the Wassermann test on the spinal fluid and the colloidal gold test, done on four patients, were negative.

An analysis of thirty cases of hypertrophic osteo-arthritis has been presented. Cervical radiculitis was found in twenty-six patients. Headache was a symptom in eight patients with cervical radiculitis, and was associated with osteo-arthritic changes in the second and third cervical vertebrae. Cervical radiculitis, with symptoms "up and down the back of the neck," was found in five patients who showed a pathologic

process in the fifth and sixth or seventh cervical vertebrae. Thirteen patients described symptoms "up and down the back of the neck," with radiation over the sides of the neck, shoulders and outer side of the arms. This group was associated with an osteo-arthritic process in the fourth, fifth and sixth or seventh cervical vertebrae. A mistaken diagnosis of thyroid disease was made in one patient.

Dorsal radiculitis, with symptoms over the distribution of the upper five dorsal roots, was found in ten patients. Diagnoses had been made of tuberculosis with pleurisy, pleurisy of the left side, angina pectoris, heart disease and cardiac neurosis. One patient had a benign cyst the size of a pea removed from the left breast, without relief of symptoms.

Fourteen patients presented symptoms of a dorsal radiculitis over the distribution of the sixth to ninth dorsal roots. Six of these complained of stomach trouble, and three had first consulted gastro-enterologists. Four patients presented pain simulating disease of the gallbladder. Of these, one had a chronic fibrous cholecystitis without stone, and was not relieved by operation; and in one patient who had a carcinoma of the gallbladder, the visceral symptoms were partially masked by the radicular pain. One case was diagnosed pleurisy of the right side. Two patients, who complained of backache across the region of the lower part of the chest, were also found to have had symptoms from the same roots over the area of the gallbladder at an earlier date.

Dorsal radiculitis with symptoms over the distribution of the tenth to twelfth dorsal roots was found in fifteen patients. Four complained chiefly of the right lower quadrant and required a differential diagnosis from chronic appendicitis. Two had been operated on for appendicitis without relief, and one had been urged to submit to an appendectomy. There was little difference in the symptoms of two patients who had submitted to appendectomy and the one who had been urged to do so and had refused. The outstanding symptom in each instance was pain. Of eleven patients who complained of bilateral pain across the lower part of the abdomen, four complained of backache across the small of the back, and two had undergone operations on the pelvic organs without relief of symptoms.

Six patients presented symptoms of a lumbar radiculitis over the distribution of the first three lumbar roots, simulating so-called meralgia paraesthetica.

Lumbar radiculitis, with symptoms over the distribution of the fourth and fifth lumbar roots, and the first two sacral roots, was found in twenty-three patients. The symptoms of this group are commonly included under the diagnosis of sciatica. Sixteen patients of this group complained of backache (pain localized over the sacrum) with sciatic

radiation, and seven complained of backache (pain localized over the sacrum) associated with pain on the inner side of the legs.

The severe upper dorsal bowing, postural deformities, neck weakness and muscle atrophies, described by von Bechterew,[1] Strümpell[2] and Marie,[3] were not observed in our patients. This study concerned, for the most part, the patient whose vertebral changes were not marked.

Hypertrophic changes in the knee, hip, shoulder or acromioclavicular joints were present in five patients. Subjective and objective sensory disturbances were present in these patients, and did not differ in any way from the disturbances observed when the process was confined to the spinal column. In one case of "poker spine" and involvement of the peripheral joints, active neurologic symptoms were minimal. The past history, however, revealed symptoms indicating a progressive involvement of various spinal nerve roots, with a subsequent quiescence during a period of thirty-five years. Bilateral sensory changes could be demonstrated with the cotton tuft. The x-ray examination revealed a mixed process consisting of the ordinary spur formations, atrophy of the bodies of the vertebrae, and calcification of the anterior ligaments.

Pain in the spinal column, localized to several vertebrae, as elicited by heavy percussion in Pott's disease and in new growths of the cord and vertebrae, was not found in this study. The root pain seen in this series was in no instance as severe as that seen in the former two conditions, and it lacked the spontaneity of the pain seen in tumors of the cord and vertebrae. Although symptoms interfered with sleep, in no case did the patient find relief by walking the floor or sleeping in a chair, as occurs in patients with new growths of the vertebrae and spinal cord. This fact was stressed by Parker and Adson.[12] Such maneuvers invariably aggravated the symptoms in our patients. The skin, overlying the spinous processes, was sometimes tender when the spinal roots to that particular cutaneous area were involved. Root symptoms and radicular sensory alterations were constantly associated with osteo-arthritic changes in the adjacent vertebrae.

DIAGNOSIS

The diagnosis of the radicular syndrome associated with spinal osteo-arthritis resolves itself into a careful history-analysis in which the symptom-bearing areas have been accurately determined, and their distribution compared with that of the spinal roots and the peripheral nerves. The radicular syndrome is characterized by distribution of symptoms according to spinal roots. The sensory alterations are also distributed according to the topography of the spinal roots. Bilateral sensory changes can be demonstrated with the cotton tuft. The presence of such changes, corresponding to the spinal vertebrae involved, is

diagnostic. The demonstration of alterations in the sensation of light touch, however, is not essential to the diagnosis. The outstanding characteristic of this syndrome is the relation of root symptoms to movement of the spinal column, their association with Dejerine's sign and the presence of hypertrophic osteo-arthritic changes in the adjacent vertebrae, which enter into the formation of the foramina of exit of the involved roots.

In the history of the chief complaint, the distribution of a root or group of roots is usually demonstrated accurately. These symptoms are most often the ones confused with the pain of visceral disease. The occurrence of bilateral pain, which may be greater on one side, over areas corresponding to the topography of the spinal roots, produced or aggravated by movement of the spine, as described, and associated with coughing, sneezing or straining, indicates the presence of a radiculitis. Root symptoms occurring during the day, induced by movement or protracted sitting, pain at night, which interrupts sleep and is relieved by a change of position, and a return of symptoms on awakening as the head is raised from the pillow is a characteristic and diagnostic train of circumstances. When one or more of these are found in the history of the chief complaint, or in other similar symptom-bearing areas, a tentative impression of radiculitis should be entertained. The induction or aggravation of root symptoms by one of the triad of coughing, sneezing or straining makes the presence of the radicular syndrome a certainty. The association with clinical evidence of an osteo-arthritic process furnishes presumptive evidence of the complete syndrome. Diagnostic aids of lesser value are the symptomatic relief obtained by strapping, the wearing of a supporting corset and physiotherapeutic measures, such as massage and heat.

In the differential diagnosis of simulated visceral disease, the history is most important. In the radicular syndrome associated with spinal osteo-arthritis, the history discloses other symptom-bearing areas with symptoms similar to those of the chief complaint. The distribution of symptoms is sometimes most diffuse, but is always characterized by a radicular topography. The physical examination shows varying grades of restriction of mobility in the spine, and these indicate the vertebrae which form the intervertebral foramina of the involved roots. The cutaneous areas of the roots, as determined in the history, should correspond to those regions of the spinal column showing impaired mobility. For example, symptoms over the lower part of the abdomen between the umbilicus and the inguinal ligaments are due to involvement of the tenth to the twelfth dorsal roots. Over the back, these roots supply the cutaneous area directly overlying the spinous processes of the lumbar vertebrae. The restriction in mobility should be present in the lower

part of the dorsal spinal column, since these roots emerge from the foramina between the ninth dorsal and the first lumbar vertebrae. The data of the involved roots, obtained from the history, and the restricted mobility of the spinal column, found in the physical examination, enable one to anticipate with considerable accuracy the vertebral involvement that the x-ray examination will show.

When properly done, the sensory examination with the cotton tuft will reveal alterations in sensation of a radicular nature, corresponding to the areas of subjective sensory disturbances and to the levels of the vertebral pathologic changes.

The presence of a radiculitis having been established, in the absence of syphilis, the history of diffuse root symptoms dependent on movement and associated with coughing, sneezing or straining, the diffuse sensory changes to light touch, the impaired mobility of the spine, the absence of local vertebral tenderness, the presence of cracking in the neck and other joints, the presence of Heberden's nodes and x-ray evidence of an osteo-arthritic process in the vertebrae adjacent to the involved roots establish the radicular syndrome in hypertrophic osteo-arthritis of the spine. The x-ray examination also aids in ruling out metastatic vertebral carcinoma and other destructive processes of the vertebrae and cord.

COMMENT

Hypertrophic osteo-arthritis of the spine is a common disease. It is conceivable that symptoms attending involvement of the nerve roots may be present as the sole cause of disability in the absence of visceral disease, or may coexist with visceral disease. It is not unusual to find that the radicular pain of hypertrophic spinal osteo-arthritis will bring a patient into the hospital as the chief apparent cause of disability, when a serious but less outspoken chronic visceral disease is also present, but masked by the striking symptoms of the former. On the other hand, this syndrome may simulate visceral disease and, as seen in this study, it becomes a likely explanation of the unsatisfactory results sometimes obtained in operations. Our analyses indicate that in adults over the age of 35, in whom pain is an outstanding symptom, a careful analysis of symptoms is necessary. Especially important is such an analysis when exploratory operative procedures are contemplated for the relief of vague abdominal conditions. When impaired mobility of the spine is present in regions which correspond to the cutaneous area of symptoms according to spinal roots, the radicular syndrome should be considered as an explanation of symptoms. If the radicular syndrome is present, it should be accorded a proper place in the disease picture, since it may simulate many visceral diseases, and in turn may mask the presence of visceral disease which may not be as outspoken in its symptomatology.

CONCLUSIONS

1. Hypertrophic osteo-arthritis of the spine, root pain and radicular sensory alterations are definitely to be associated as a clinical syndrome.

2. The symptoms of the syndrome are dependent on movement of the spine, relaxation of the supporting spinal musculature or coughing, sneezing and straining.

3. The syndrome is characteristic enough to permit clinical recognition.

4. The symptoms of the syndrome are independent of the visceral diseases which they simulate, and can be differentiated from the visceral diseases with which they may coexist.

THE CARDIOVASCULAR PROBLEM IN PNEUMONIA*

B. M. RANDOLPH, M.D.
WASHINGTON, D. C.

It has been repeated so often that death from pneumonia is the result of heart failure that this view seems to be accepted generally by the medical profession.[1] The frequent observation of a dilated right side of the heart, with more or less evidence of toxic myocarditis at autopsy seems to be the basis for this assumption. If it is true that the patient with pneumonia dies only because the heart muscle gives way, the clinical data observed during life should corroborate this fact. If it is not true, it is important, from the standpoint of both therapy and prognosis, that the true pathologic physiology of the disease should be understood.

The terminal dilatation of the heart is commonly believed to result from the combined effect of two factors: (*a*) the impairment of functional integrity through the injurious action of the toxins of the infection on the muscle tissue of the heart, and (*b*) the increased cardiac load resulting from obstruction to the pulmonary circulation, due to the presence of the inflammatory exudate in the lung tissue.

There can be no question that these factors exist. That they are the factors of primary importance in the clinical picture is open to doubt.

On the assumption that failure of the heart muscle is fundamental in mortality from pneumonia, there has grown up a therapy that is widely practiced in the United States, namely, the routine administration of digitalis.[2] This practice has become much more general since the World War. From my experience and from the observation of the work of my colleagues, I have formed an opinion that is at variance with the one commonly accepted. This opinion is that the routine treatment with digitalis for pneumonia is ineffective; that not infrequently it is injurious, and that it is based on a failure to apprehend important factors in the pathologic physiology of the disease.

Before presenting the data on which my views rest, it is proper to state that in the District of Columbia and the nearby regions the bacterial agent found in the majority of cases of pneumonia has been *Streptococcus hemolyticus* or *viridans*, or the two combined, rather than any of the pneumococci. This has been true since 1916, at which time I began to have cultures of sputum made in my cases as a routine pro-

* Submitted for publication, July 15, 1928.

1. Billings, F. T.: Am. J. M. Sc. **171**:872 (June) 1926.

2. Burrage, W. S., and White, P. D.: Am. J. M. Sc. **174**:260 (Aug.) 1927.

cedure. Other local clinicians are finding out the same thing. The idea is rather prevalent that lobar pneumonia is pneumococcus pneumonia; for it is assumed without making a culture of the sputum that if inflammation of the lung is primary and has a lobar distribution, it is of pneumococcic origin.

Such is not the case. Pneumonia of abrupt onset occurs which has a typical lobar distribution, so far as physical examination can determine, in which cultures from the sputum do not show pneumococci but streptococci. The presence of pneumococci has been assumed merely on the basis of the examination of a stained smear of the sputum. The method followed in the laboratory of the George Washington University consists in the selection of a specimen of the first sputum coughed up from the lungs, which usually contains blood; cultivation and subcultivation on different mediums, with inspection of the resulting colonies; further differentiation by tests of bile solubility, inulin fermentation, agglutination reactions and mouse pathogenicity. Under this scrutiny it is found that not a few organisms which from the morphology seen in the smears appear to be pneumococci are streptococci. Conditions are different farther north. In a series of 2,000 cases, Cecil,[3] of New York, found that 95.6 per cent were due to the pneumococcus and 3.8 per cent to the streptococcus.

REVIEW OF 100 CASES

A review of 100 cases occurring in the George Washington University Hospital has been made. The cases are consecutive, with the exception of the omission of those cases in which complicating and terminal pneumonia was present, those in which there was a possible doubt of the correctness of the diagnosis and those in which the record was not sufficiently complete for the purposes of the study.

This hospital is, so far as its private rooms are concerned, an open hospital, and about half the cases reviewed occurred in the practice of a relatively large number of physicians not connected with the hospital staff. The data afforded, therefore, do not furnish a basis for a thorough clinical study. They represent, however, a considerable variety of therapeutic procedure, the investigation of which was the primary object of the review. The result shows that the aphorism of Loomis, uttered more than forty years ago, is as true today as it was then, namely, that there are some patients with pneumonia whom one cannot cure; some whom one cannot kill, and a certain proportion whom wise treatment and good nursing will help to recover.

3. Cecil, R. L.: Tr. Assoc. Am. Physicians **41**:208, 1926. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Lobar Pneumonia, Arch. Int. Med. **40**:257 (Sept.) 1927. Cecil, R. L.: The Specific Treatment of Lobar Pneumonia, Arch. Int. Med. **41**:322 (March) 1928.

Digitalis was prescribed for thirty patients of this series as soon as the disease was recognized as pneumonia. In this group there were seven deaths, a mortality rate of 23.3 per cent (table 1). For few patients was the dosage sufficient to produce a full digitalis effect. Often it seems to have been given because it was considered the proper thing to do rather than because there was any clear idea of what was to be accomplished.

In thirty-four cases, the use of digitalis was instituted later in the course of the disease. In this group there were eight deaths, a mortality of 23.53 per cent (table 2). It is manifest that these figures do not furnish a proper basis for the comparison of the merits of early and later institution of treatment with digitalis. The physician who from the beginning of the disease uses digitalis therapy as a routine measure will use this treatment for many patients who would recover without the drug. The physician who does not use digitalis until the condition of the heart seems to demand it will employ it only in the graver cases. Not infrequently the drug is prescribed at the instance of a consultant who is not called in until the patient has begun to get worse.

In thirty-six cases digitalis therapy was not used; four deaths occurred, a mortality rate of 11.1 per cent (table 3). This group included a large majority of the mild cases, and no statistical value can be attached to the therapeutic results. Details of the cases reviewed are presented in the accompanying tables and charts.

It is apparent, therefore, that statistics on drug therapy that do not take into consideration all the factors presented by the individual patients cannot be relied on. It has always been recognized that advanced age tends to make the prognosis in pneumonia unfavorable. Other unfavorable factors are pronounced hypertension and obesity. The presence of some other chronic disease and especially the early and complete cooperation of the patient are individual factors of importance. Again, there is such a variation in the severity of individual cases that the statistical method of study presents too many sources of error to be trustworthy. I believe that progress in the understanding and management of this disease is made through careful observation and records by competent students of the clinical and laboratory phenomena.

My observations have led me to believe that the primary toxic effect on the circulatory system is exerted on peripheral blood vessels through the vasomotor system, and that failure of the myocardium is secondary or terminal. This view is based on the early depressant effect of the infection on the blood pressure, which depression runs parallel with the increasing gravity of the prognosis, and on the utter failure of digitalis to control the rate of the heart even when the drug is given in full dosage from the beginning. Furthermore, death from pneumonia may occur as a result of respiratory paralysis without myocardial failure. The

ordinary course of the fatal case is as follows: For several days the pulse is of a fairly good quality and the blood pressure relatively constant, though the latter is reduced below normal; then, often abruptly, the pulse increases in rate, becomes weak and sometimes irregular, and loses the tone which it has hitherto maintained. The blood pressure at that time shows a marked fall, the diastolic often more proportionally than the systolic. The cardiac impulse becomes diffuse, and the quality of the heart tone is impaired. Unless therapeutic measures are successful in restoring circulatory balance, death ordinarily ensues in twelve hours, or even less. Autopsy shows the heart dilated, but histologic study does not show such deterioration of the heart muscle as toxic failure of the heart would lead one to expect; for example, as that seen in heart failure in cases of diphtheria.

A more reasonable explanation of the circulatory failure occurring in pneumonia would appear to be as follows:

1. There is an oxygen hunger of the tissues due to an elevation of the level of conversion of carbondioxide-hemoglobin into oxyhemoglobin; probably an alteration in the blood, which is the essential physiologic defect caused by the disease.

2. The increased respiratory rate and increased functional demand on the heart for oxygenated blood result in an accelerated and exaggerated heart action.

3. The lowered blood pressure places an additional tax on the heart in its effort to carry on circulation without an adequate peripheral tone to support it.

4. The right side of the heart is further incommoded by the resistance to the pulmonary circulation offered by the presence of the exudate in the lung.

5. Last, but perhaps not least, the heart muscle itself does not get properly oxygenated blood for its adequate nutrition.

The therapeutic need of the overtaxed heart, if one is to conserve its integrity, is not for something to increase the amount of work it is doing, as it is already working harder than it should, but rather for treatment directed toward lessening the functional load. If digitalis were effective in slowing the rate of the heart in pneumonia, one should have a logical reason for its employment, that is, lengthening the rest period; but I have never found that it does this. It increases the contractile effort of the ventricular muscle, thus tending to use up its reserve more rapidly. I consider that the indication for digitalis therapy in pneumonia is the same as in other conditions, namely, when failure of the heart muscle begins. When this occasion arises, if considerable doses of the drug have been given over several days, one dares not use the large doses required to meet this emergency for fear of exceeding the limit of tolerance.

On the basis of present knowledge, specific immunizing therapy is applicable only to a limited number of cases of pulmonary inflammation (pneumococcus type I). It seems that there is a prospect that a practical technic for the specific treatment of conditions due to types II and III will be provided.[4] Up to the present time, however, conspicuous and consistent failure has attended efforts to provide a successful specific therapy for streptococcic infections. It seems, therefore, that work will have to be continued along the line of conserving the vital forces in these cases until the activity of the infection has spent itself.

The therapeutic indications presented by the circulation in pneumonia are: (1) to lower the toxemia, with a view to restoring the oxygen carrying capacity of the blood; (2) to increase the conversion of carbondioxide-hemoglobin into oxyhemoglobin, and (3) to sustain the blood pressure, thus relieving the heart as far as possible from the increased labor entailed by the effort to carry on the circulation unsupported by an adequate peripheral resistance.

I believe that helplessness in severe cases of pneumonia arises largely from one's inability to influence in any dependable way the pathologic elevation of the oxyhemoglobin threshold, which interferes with the necessary interchange of oxygen in the lungs. It is not known what causes this: whether it is an alteration in the red cell itself, in the blood serum or in both. The acid concentration theory, advanced by some investigators, if correct, should have led to a ready control of the situation through alkaline therapy. But there is some factor present that cannot be explained by the theory of quantitative alterations in the hydrogen ion concentration or in the alkali reserve. Nevertheless, a rather large experience in the use of the citrates and acetates of sodium and potassium in streptococcic infections of the respiratory tract has given me the impression that when administered early they have some effect in modifying the intensity of the infectious process and in lessening the frequency of extensions and complications to an extent not accomplished by other diuretics. There is urgent clinical need of research in the laboratories of biophysics and biochemistry in order to determine just what are the essential factors in pneumonia that cause the failure of the blood to take oxygen from the air in a normal fashion.

It is here that blood-letting seems to offer its most useful rôle. I believe that it accomplishes more than a mere mechanical relief of the load on the right side of the heart. I have not found that the best results from phlebotomy are obtained when its use is deferred till the heart shows signs of failure, though even then it is sometimes found to be a life-saving measure. In acutely toxic cases early phlebotomy has

4. Cecil (footnote 3, third reference).

immediately improved the clinical picture, subjective and objective, and patients have gone on to recovery without causing further serious anxiety. If the blood-letting is deferred until the blood pressure has collapsed, benefit is not derived from it. The effect on the toxic state has seemed to be analogous to that which I have observed in venesection in sunstroke. Subjectively, the patient becomes more comfortable almost immediately. The respiration becomes more regular and is conducted with less effort and distress. I have had an exhausted patient go to sleep while the blood was flowing. Shortly after the flow begins, the pulse is felt to have undergone an alteration, becoming fuller, softer and losing its tense, thready quality. The systolic blood pressure does not show a marked change, sometimes falling from 5 to 10 mm., sometimes remaining stationary. In one case complicated by mitral stenosis I noted a rise of 10 mm. during the flow of blood. The diastolic blood pressure, if lower than normal, often shows a tendency to rise during the venesection, with a further rise later.

I do not believe that phlebotomy should be undertaken in pneumonia with the idea that a definite amount of blood must be withdrawn at one time. Ordinarily, I take from 300 to 600 cc. from an adult. The pulse is the guide which tells one when to stop. As the blood flows, the full wave, previously described as being established soon after the procedure is begun, is abruptly interrupted by a weakened subtonic wave. At this point the tourniquet should be loosened and the blood-letting stopped.

In certain cases, the inhalation of oxygen seems to be effective in keeping the anoxemia within the limits of tolerance. Occasionally, I see a patient in whom the relief obtained is almost dramatic. In other cases, continuous or intermittent inhalation of oxygen over a long period appears to enable cyanotic patients to hang on till the disease has spent itself. More frequently, however, this treatment has failed to change the clinical picture materially, no matter how high the concentration of oxygen. The blood defect that I have spoken of appears to reach such a degree that carbon dioxide conversion cannot be carried on, no matter how high the concentration of oxygen. I have never had access to an oxygen chamber; so I have had no experience with this method of administration of the gas.[5]

Working on the hypothesis that the circulatory failure occurring in pneumonia is primarily peripheral, and that the myocardial failure is secondary, I have recently made some observations on the behavior of patients in cases in which the therapy was directed toward sustaining the vasomotor tone. Pituitary was the agent selected. Epinephrine

5. Barrach, A. L.: Acute Disturbance of Lung Function in Pneumonia, J. A. M. A. **89**:1865 (Nov. 26) 1927.

was rejected, partly because its action is too transient, and partly because it increases the contraction of the heart muscle.[6] Ephedrine was considered, but I did not think that I knew enough about its pharmacologic or its toxicologic actions to justify its use. The extent of my observations is not sufficient to warrant definite conclusions, but I believe that they show effects that are suggestive and therefore worth recording.

DIFFUSIBLE AND OTHER STIMULANTS

In my experience, caffeine is ineffective as a stimulant to the circulation in pneumonia. I have never seen any clear evidence that its administration accomplishes any good. I have seen patients who had received repeated doses over some time exhibit insomnia and restlessness that amounted almost to delirium; these symptoms subsided when the administration of caffeine was discontinued.

The same may be said of strychnine as of caffeine.

Camphor administered hypodermically in oil apparently affords a brief period of stimulation, which occasionally tides over a critical period. If this effect is not prompt and definite, nothing will be accomplished by repeated dosage.

The stimulant effect of ammonia is too weak and too transient to be of material value.

Of the benefit derived from whisky, I have a definite empiric conviction. Its good effect does not appear in all cases. It is valuable for elderly persons; for those habituated to its use, it is more so. I am unable to explain entirely its physiologic action. Its hypnotic action in a disease in which rest and sleep are so important is undoubtedly valuable, often lessening the need of opium derivatives. It induces a sense of comfort and serenity in the patient, which is not a handicap in the fight with the disease. Its food value may be a factor, but the quantity administered seems too small for this to explain the whole matter. A definite beneficial effect on the pulse is often noted. A fuller, softer, more adequate beat replaces the irritable subtonic one. In spite of the myriads of pages written on the subject of alcohol, there may still be something to learn about it.

The accompanying tables, giving the details of the cases of the series, require further comment. Virulence is rated as mild, moderate, severe, severe plus and severe double plus.

It was mild in those cases in which there was a definite clinical picture and recorded physical signs establishing the diagnosis of pneumonia but in which the patients were not at any time sufficiently ill to give serious concern as to the outcome of the disease. The virulence

6. Cushny, A. R.: Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1918, p. 368.

TABLE 1.—*Patients Receiving Digitalis on Admission to Hospital*

Number	Age	Virulence	Maximum Leukocyte Count	Days from Onset to Admission	Daily Digitalis Dosage, Gm.	Result	Bacteriology of Sputum	Remarks
1	37	Moderate	26,000	2	0.27	R	.....	Empyema; pneumonia followed grip
2	38	Severe	21,000	?	0.3	R	Streptococcus hemolyticus	
3	69	Moderate	19,600	1	0.55 (5 days)	D	Pneumococcus	Hypertension and alcoholism
4	18	Severe	18,600	1½	0.27	R		
5	55	Moderate	26,800	?	0.33	R		
6	19	Severe	32,600	1	0.33	R		
7	35	Severe	7,400	5	0.55	R	Streptococcus hemolyticus and viridans	Diagnosis confirmed by x-ray; pleural effusion
8	6	Severe	24,000	?	0.1	R		
9	42	Moderate	13,000	4	0.25	R		
10	37	Severe	24,400	4	0.2	R		
11	66	Moderate	25,000	?	0.33	R		
12	58	Moderate	24,200	7	0.4	R	Streptococcus viridans	
13	28	Severe ++	21,800	1	0.53	R	.....	Complicated by otitis media; phlebotomy seemed life-saving
14	84	Severe ++	8,800	1	0.55	D	.....	Died on fourth day
15	52	Severe	17,000	?	0.8	R	Streptococcus hemolyticus and viridans; pneumococcus	Pneumonia followed acute bronchitis of two weeks' duration
16	65	Severe +	27,800	9	0.27	D	Streptococcus viridans and hemolyticus	Admitted in an advanced stage
17	41	Severe +	19,800	2	0.6	D	Pneumococcus and Streptococcus hemolyticus	Pneumococcus on second culture; two days after, Streptococcus hemolyticus
18	27	Severe +	24,000	2	0.4	R	Streptococcus hemolyticus and viridans	
19	30	Severe +	28,600	2	0.6	R		
20	25	Severe +	20,200	1	0.4	R		
21	55	Severe	15,000	4	0.4	R	Streptococcus hemolyticus and viridans	
22	16	Severe +	10,000	4	0.6	R	Streptococcus viridans	Strophanthin, 0.64 mg. by hypodermic on admission
23	14	Severe	40,000	5	0.33	R	.....	Empyema
24	21	Severe +	20,200	3	0.8	R	Streptococcus hemolyticus	
25	58	Moderate	16,100	2	1.1	R		
26	14	Severe +	30,000	3	0.4	D	Streptococcus hemolyticus and viridans	Late involvement of opposite lung
27	56	Severe +	40,750	2	0.6	D	Streptococcus hemolyticus and viridans	
28	45	Severe	24,050	?	0.15	R		
29	50	Severe	16,400	6	0.4	D	Streptococcus viridans and hemolyticus	Empyema
30	..	Severe +	20,200	1	Chart 6	R	Streptococcus viridans; pneumococcus and streptococcus hemolyticus	

Total number of cases, 30; deaths, 7; mortality, 23.33 per cent.

TABLE 2.—*Patients in Whom Digitalis Therapy was Instituted Later than Date of Admission*

Number	Age	Virulence	Maximum Leukocyte Count	Digitalis Begun, Day of Disease	Daily Digitalis Dosage, Gm.	Result	Bacteriology of Sputum	Remarks
1	72	Moderate	19,400	3d	0.25	R		
2	55	Severe	33,000	4th	0.2	R		
3	45	Moderate	21,000	4th	2.6	R	Streptococcus hemolyticus	
4	64	Moderate	17,800	4th	0.4	R	Streptococcus viridans	
5	29	Severe	17,200	4th	0.27	R		
6	58	Moderate	27,000	3d	0.27	R		
7	65	Moderate	14,800	4th	0.4	R		
8	50	Severe	26,400	6th	0.63	R		
9	45	Moderate	16,400	5th	0.53	R		
10	31	Severe	23,000	3d	0.4	R	Streptococcus viridans and hemolyticus	
11	78	Moderate	22,600	4th	0.4	R		
12	53	Severe	24,000	2d	0.33	R	Pneumococcus; Streptococcus viridans and hemolyticus	
13	29	Severe	23,200	7th	0.6	R	.....	Relapse on fifth day
14	32	Severe +	18,800	3d	0.4	D	Streptococcus hemolyticus	
15	17	Severe +	38,000	7th	0.6	R		
16	28	Severe	24,400	2d	0.6	R	Pneumococcus and Streptococcus hemolyticus	
17	81	Severe	37,000	2d	0.6	D	.....	Chronic hypertension
18	25	Severe	22,400	3d	0.4	R		
19	16	Severe +	26,600	3d	0.4	R		
20	76	Severe +	.....	2d	0.4	D		
21	58	Severe	24,800	4th	0.4	R		
22	40	Severe	.....	5th	0.4	R		
23	36	Severe +	30,400	6th	0.4	R	Streptococcus viridans and hemolyticus	Phlebotomy and whisky seemed the effective therapy
24	26	Moderate	18,050	2d	0.27	R	Streptococcus viridans and hemolyticus	
25	47	Moderate	36,850	8th	0.8 in 12 hours	R	Streptococcus viridans and hemolyticus	Pituitary (4 doses), with digitalis; impending collapse
26	30	Mild	10,400	5th	0.33	R		
27	..	Moderate	24,000	2d	0.5	R	Streptococcus viridans	
28	..	Moderate	18,400	8th	0.27	R		
29	67	Severe	22,000	4th	0.2	R	.....	Complicated by chronic pathologic condition in gall-bladder region, the nature of which was not determined
30	34	Severe ++	36,300	2d	Chart 1	D	Streptococcus hemolyticus and viridans	Autopsy showed multiple abscesses in both lungs
31	39	Severe	35,850	3d	Chart 2	D	Streptococcus hemolyticus and viridans	Complicated by active secondary syphilis
32	55	Severe +	21,500	2d	Chart 3	D	No sputum	Extremely obese; treated 4 years for hypertension (200+)
33	19	Severe ++	34,950	3d	Chart 4	D	No sputum	Overwhelming intoxication
34	26	Severe ++	19,700	2d	Chart 7	D	Streptococcus viridans and hemolyticus	

Total number of cases, 34; deaths, 8; mortality, 26.53 per cent.

TABLE 3.—*Patients Treated Without Digitalis*

Number	Age	Virulence	Maximum Leukocyte Count	Result	Therapy	Bacteriology of Sputum	Remarks
1	27	Mild	15,500	R	Sodium citrate; 8 Gm. daily	Pneumococcus	
2	38	Mild	13,000	R	Sodium citrate; 6 Gm. daily	.....	
3	18	Mild	18,000	R	Symptomatic	Streptococcus viridans	Pneumonia followed tonsillectomy
4	52	Severe	26,000	R	Diuresis	Streptococcus viridans and Streptococcus hemolyticus	
5	53	Severe	15,800	R	Sodium citrate; 8 Gm. daily		
6	58	Mild	22,000	R	Ammonium chloride; whisky; sponge baths		
7	79	Mild	36,000	R	Initial; dovers powder; symptomatic		
8	..	Severe	26,000	R	Inital catharsis; symptomatic		
9	65	Moderate	11,000	R	Sodium citrate	Pneumococcus	
10	18	Severe	37,200	R	Sodium citrate; 8 Gm. daily		
11	20	Mild	13,000	R	Creasote, calcium and ammonium salts	Streptococcus viridans	
12	21	Mild	17,800	R	Catharsis; symptomatic		
13	27	Mild	26,000	R	Ammonium chloride; symptomatic		
14	32	Mild	18,400	R	Symptomatic	Streptococcus viridans and hemolyticus	
15	75	Mild	16,000	R	Initial; dovers powder; sodium citrate, 8 Gm.		
16	16	Mild	22,600	R	Sodium citrate; 6 Gm. daily		
17	29	Severe	28,000	R	Symptomatic	Pneumococcus 4, and Streptococcus hemolyticus	
18	21	Severe	21,800	R	Urotropin; creasote		
19	38	Severe	11,400	R	Sodium citrate; 6 Gm. daily	Streptococcus hemolyticus and viridans	
20	40	Mild	14,600	R	Urotropin		
21	46	Severe	19,800	D	Catharsis; cough mixture and whisky	Streptococcus viridans and hemolyticus	Followed afebrile bronchitis of ten days' duration
22	14	Severe	24,400	R	Quinine	Streptococcus viridans and pneumococcus	Followed otitis media
23	64	Mild	23,400	R	Initial catharsis; sodium citrate, 4 Gm.	Streptococcus hemolyticus and viridans	Diagnosis confirmed by x-ray
24	28	Mild	.....	R	Sodium citrate; 12 Gm. daily	Streptococcus hemolyticus and viridans	Diagnosis confirmed by x-ray
25	38	Moderate	18,800	R	Symptomatic		
26	30	Mild	13,200	R	Symptomatic	Streptococcus hemolyticus and viridans	
27	38	Mild	12,400	R	Symptomatic	Streptococcus hemolyticus and viridans	Followed bronchitis; diagnosis confirmed by x-ray
28	..	Severe	16,400	R	Sodium citrate	Streptococcus viridans and hemolyticus	Complicated by active syphilis
29	54	Severe +	22,000	D	Sodium citrate, 8 Gm. daily; caffeine	Pneumococcus	Obese and unmanageable
30	36	Severe ++	.....	D	Symptomatic	.....	In extremis on admission
31	55	Severe ++	34,600	R	Transfusion	Pneumococcus 2	Blood stream infection
32	65	Severe +	11,350	D	Symptomatic	.....	In extremis on admission
33	37	Mild	12,750	R	Symptomatic	Streptococcus hemolyticus and viridans; Bac. mucos capsulat.	
34	43	Severe	11,250	R	Sodium citrate; phlebotomy	.....	Diagnosis confirmed by x-ray (chart 5)
35	48	Severe	12,700	R	Potassium acetate	Streptococcus hemolyticus and viridans	
36	38	Severe	26,200	R	Urotropin; acetylsalicylic acid		

Total number of cases, 34; deaths, 8; mortality, 26.53 per cent.

was considered moderate in those cases in which the patients were acutely ill at the outset but improved steadily and made an uneventful recovery, and severe in those cases in which serious concern as to the prognosis was felt. Severe plus virulence was present in those cases in which the patients were so gravely ill that a fatal issue was expected, and severe double plus in cases in which there was overwhelming intoxication or grave complications.

Tincture of digitalis begun and continued throughout; total, 52 grains
Administration of pituitary begun and continued throughout; total, 25 ampules

CHART 1 (case 1).—The blood pressure was maintained apparently by the administration of pituitary.

A complete presentation of the treatment given these patients could not be made without reporting the individual cases. Alkaline diuretics were used in many cases, the dosage being limited by the appearance of alkaline urine; in a large majority opium derivatives were used at some time for pain, cough or restlessness. Various counterirritants to the chest were frequently used, mustard being the favorite. Occasionally an ice bag was placed on the chest of a patient. A considerable number were given more or less systematic hydrotherapy in the form of sponge baths. Caffeine was used in circulatory failure by nearly all physicians, whether or not digitalis was being given.

In giving the bacteriology of the sputum, I state first the predominating organism and then the others in the order of the number of colonies present.

REPORT OF CASES

CASE 1.—A man, aged 34, was admitted to the hospital on the second day of the disease, which was severely toxic from the onset. There was pneumonia of the lower lobe of the right lung. Cultivation of the sputum resulted in *Streptococcus hemolyticus* predominating, and *Streptococcus viridans*. The leukocytes

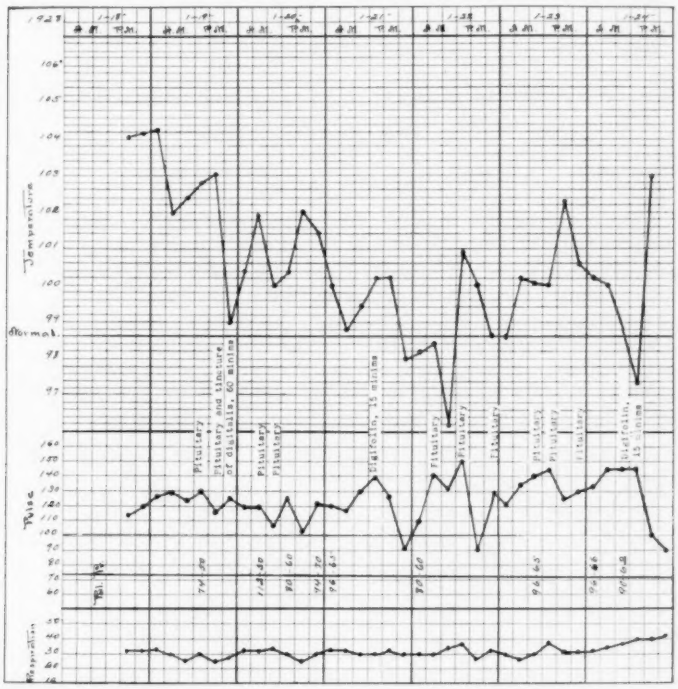

CHART 2 (case 2).—Death occurred from the extension of the disease following effort.

numbered 36,300. The patient showed good resistance until the fifth day, at which time invasion of the left lung was noted. He was treated with digitalis and pituitary, receiving 33 grains (2.16 Gm.) of the former and 16 ampules of the latter. It was noted that his blood pressure was well sustained until the day of death, which occurred on the twelfth day. Autopsy showed bronchopneumonia of both lungs, with multiple small abscesses; also active tuberculosis of both upper lobes, a recent recrudescence (chart 1).

CASE 2.—A man, aged 39, was admitted to the hospital on January 18. The evening before he was admitted, he was seized with pain in the right side of the chest, cough and weakness. He was found to have pneumonia involving the middle

lobe of the right lung and the lower lobe of the left lung, and also an abundant eruption of secondary syphilids. The blood showed: leukocytes, 35,850, with 90 per cent polymorphonuclears. The Wassermann reaction was 4 plus. The blood culture was negative. A sputum culture showed *Streptococcus viridans* predominating and *Streptococcus hemolyticus*. The extremely low blood pressure which existed on admission seemed to respond favorably to the administration of

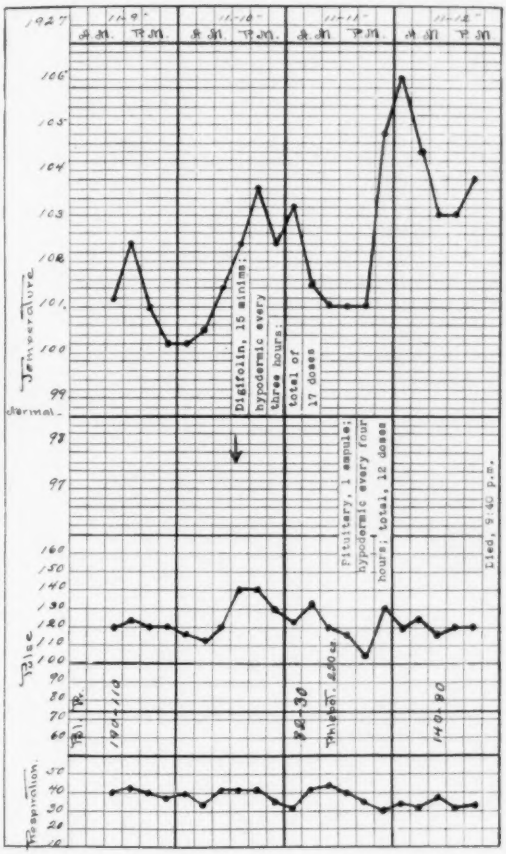
Temperature
Pulse
Respiration
Digifolin, 15 minims, hypodermic every three hours; total of 17 doses
Pituitary, 1 ampule, hypodermic every four hours; total, 12 doses
Died, 9:40 p.m.

CHART 3 (case 3).—Death occurred from toxic respiratory paralysis; the heart function was maintained.

pituitary. On the fourth day, he appeared to be doing well, and I ordered an x-ray picture made of the lungs. During this procedure, he was subjected to more effort than is usual in such cases, and this was promptly followed by an invasion of the lower lobe of the right lung, which proved fatal. Autopsy showed pneumonia of the middle lobe of the right lung and the lower lobes of both lungs, while the x-ray picture did not show any involvement of the lower lobe of the right lung.

proving that the extension occurred after the picture was taken. It is possible that the concurrent syphilitic infection may have been a factor in the extremely low blood pressure observed in this case (chart 2).

CASE 3.—A woman, aged 55, seen in consultation with Dr. Hyde, was admitted to the hospital on November 9. She had been under treatment for high blood pressure for four years, the systolic reading being constantly above 200. Two days before

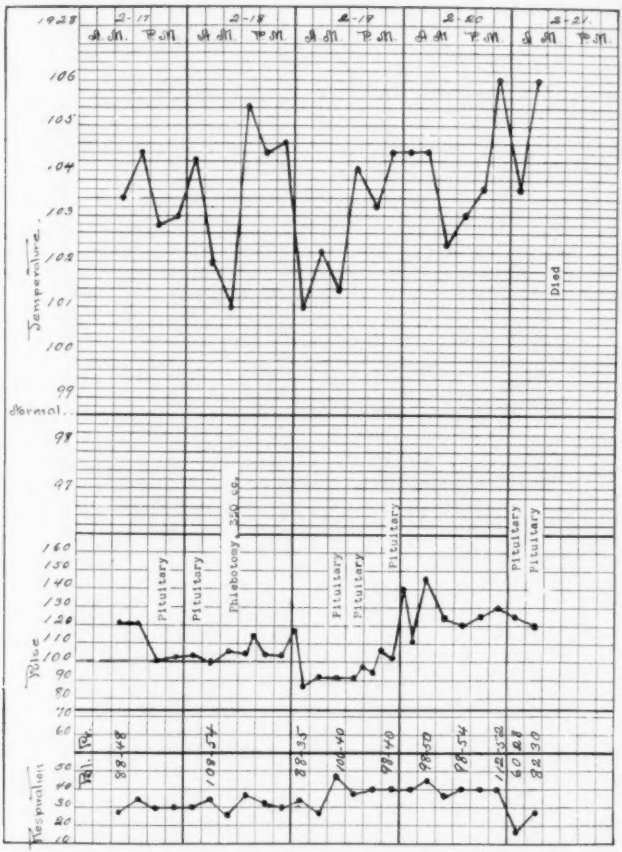

CHART 4 (case 4).—Death resulted from toxic respiratory paralysis; the blood pressure was maintained nearly to the end.

admission, she suddenly developed sharp pain in the precordium, which radiated to the epigastrium. It soon became less sharp and developed into a steady ache. She was seen the following day by Dr. Hyde, at which time the systolic pressure was 200. He found pneumonia of the lower lobe of the left lung. When she was admitted to the hospital she was extremely ill, and an unfavorable prognosis was given at the outset. The leukocytes numbered 24,500, with 84 per cent polymorpho-

nuclears. Treatment with a digitalis preparation was begun on the second day. There was little change in her condition until the third day, when she went into collapse, with a rapid fall of blood pressure. A phlebotomy was done, and pituitary treatment was instituted. She appeared to be dying at the time, but rallied, and survived until the following day, when she died of respiratory failure. In this case the inhalation of oxygen was effective in improving the dyspnea and cyanosis for a time (chart 3).

CASE 4.—A robust young mechanic, aged 19, was admitted to the hospital on February 17. He was too ill to give a history, and none was obtainable. He had

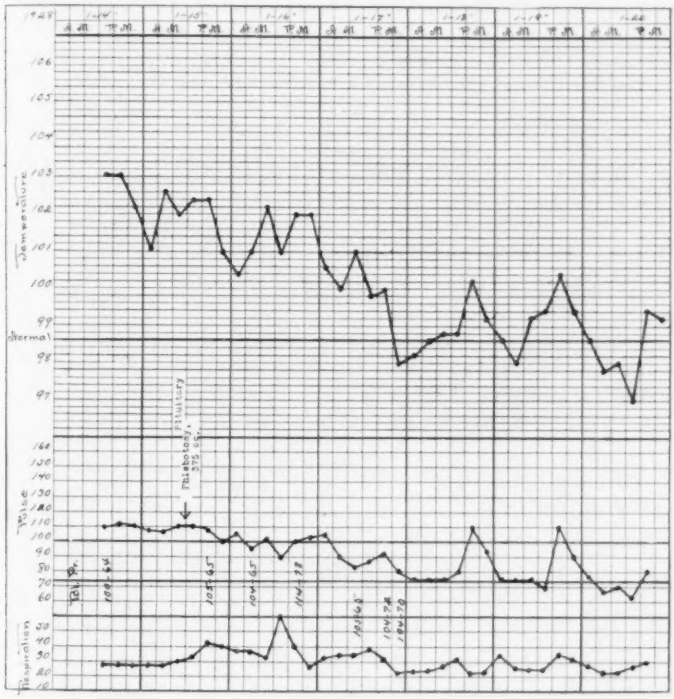

CHART 5 (case 5).—The patient was evidently benefited by early phlebotomy.

worked until thirty-six hours before admission. He had pneumonia of the lower and middle lobes of the right lung. The leukocytes numbered 34,950, with 89 per cent polymorphonuclears. The urinary chlorides were absent. He had a harassing cough, but did not raise any sputum. Marked dyspnea and cyanosis were present. It was manifest from the outset that an overwhelming intoxication was present. He died on the fourth day after admission. Autopsy was refused.

Phlebotomy gave temporary relief from the dyspnea. The day before death there were signs of invasion of the left lung. At the same time evidence of beginning myocardial failure was noted, namely, a diffuse wavelike impulse and a diminution of the muscular tone of the heart sounds. In spite of the malignant

character of the infection, pituitary seemed to maintain the blood pressure at a higher level than that shown when he was admitted (chart 4).

CASE 5.—A white man, aged 42, was admitted to the hospital on the third day of the disease; he was severely toxic, with great distress in breathing. There was pneumonia of the upper and middle lobes of the right lung. The leukocytes numbered 11,250. The sputum showed streptococci, but no pneumococci. Conspicuous subjective relief followed phlebotomy. The patient's circulation did not require supportive treatment after the second day in the hospital. Chart 5 shows

Administration of digitalis from onset until
Pulse rate weak and irregular, administration of digitalis stopped
Pituitary
Pituitary
Pituitary

day (chart 6). The patient received digitalis from the outset, 4½ grains (0.29 Gm.) daily for two days, and then 6 grains (0.4 Gm.) daily until the eleventh day. She began to show evidence of weakening circulation on the eighth day, at which time a single dose of pituitary was given. On the tenth day she was worse, and the prognosis was grave. On the eleventh day, the use of digitalis was discontinued, and vigorous administration of pituitary was instituted. Chart 6 shows the results.

The patient made an ultimate recovery. This case shows that a circulation which is failing under digitalis therapy may become reestablished when that therapy is discontinued.

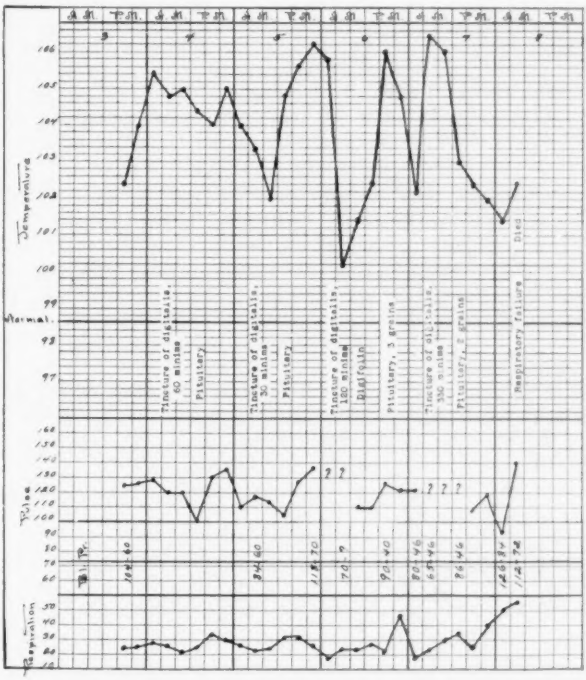

CHART 7 (case 7).—Death occurred as a result of toxic respiratory paralysis; the heart function was maintained throughout.

CASE 7.—A robust woman, aged 26, mother of seven children, at the time the present illness began was nursing an infant, aged 5 months. Three days before admission she began to have pains in the chest and back. The next day she had a severe chill, which was followed by fever. On that day and the next she had nausea and vomited. She was admitted to the hospital on the second day after the chill, extremely ill, cyanosed and with a bright red, sharply defined flush on both cheeks. There was severe cough, and she had pain in the right side of the chest. Physical examination indicated consolidation of the lower lobe of the right lung and slight enlargement of the liver and spleen. The leukocytes numbered

19,800, with 88 per cent polymorphonuclears. There was a bloody expectoration, which on culture showed *Streptococcus viridans* and *Streptococcus hemolyticus.*

Early in the morning of the sixth day she had a collapse, accompanied by profuse sweating, and a pulse rate so rapid, weak and irregular that it could not be counted accurately. There was also Cheyne-Stokes breathing. I thought at the time that I was dealing with the crisis of a pneumococcus infection, as I had not yet received the report from the sputum culture. Under stimulation there was a temporary improvement in the circulatory efficiency, but the patient died on the eighth day after the onset of respiratory failure. Dr. Moore, house physician, was present at the death, and noted that the heart continued to beat for some time after the respiration had finally ceased. He did not time this period, but estimated that it must have been nearly half a minute (chart 7).

The entire clinical picture presented by this patient, except the temperature curve, was identical with that observed in pneumococcus pneumonia.

At autopsy, pneumonia of the lower and upper lobes of the right lung was found. There were also: toxic hepatitis, a mild acute splenic tumor, toxic nephrosis, toxic myocarditis and terminal dilatation of the heart on both sides. There was a terminal hypostatic congestion of the left lung. A blood culture from the central portion of the pneumonic area showed a pure culture of *Streptococcus viridans.*

CONCLUSION

It is realized that much of the matter presented in this article is an expression of opinion, and as such is open to question. My chief purpose in this paper is to question the opinions which are commonly accepted.

It is possible that the difference in the bacteriology of my cases from that of most cases of pneumonia reported may be a factor in the difference in the reaction to therapeutic measures. The behavior of the circulation in pneumococcus pneumonia, however, has not led me to consider the involvement of that system as materially different from that which seems to occur in streptococcus pneumonia.

An important difference is that in inflammation of the lungs caused by streptococci one is not dealing with an eight day infection which can be expected to terminate by crisis at a given time. The duration is inconstant and the defervescence is gradual (as a rule); extension of the disease and relapse may occur at almost any stage. The therapeutic problem, therefore, is not merely the sustaining of the vitality of the patient till a definite crisis is passed. This fact seems to make conservatism in the use of myocardial stimulants more important.

To attempt to combat the collapse of the peripheral circulation seems to be a sound principle in the therapy for pneumonia. My observation has not been sufficiently extensive to speak positively of the value of pituitary for this purpose. I believe that something beneficial has been accomplished in some patients, and this opinion is shared by others who have been associated with me. It manifestly does not have a beneficial effect on the toxemia. So far I have not seen any ill effects that I could attribute to the drug.

IMPAIRED AURICULOVENTRICULAR CONDUCTION IN RHEUMATIC FEVER

A COMPARATIVE STUDY WITH DIAGNOSTIC APPLICATIONS *

ROBERT L. LEVY, M.D.
AND
KENNETH B. TURNER, M.D.
NEW YORK

It is now well known that auriculoventricular conduction is frequently impaired in the course of rheumatic fever and that this disturbance affords valuable evidence of myocardial involvement.[1] In a number of instances of partial or complete heart block [2] and in one case showing only prolonged auriculoventricular conduction,[3] postmortem examination of the heart has disclosed characteristic rheumatic lesions involving the auriculoventricular node or bundle. Such lesions have consisted of cellular infiltration and edema during the acute stages of the disease, or of scar tissue after healing has taken place. The transitory nature of conduction disturbances in many cases indicates that the inflammatory process may subside without graphic evidence of permanent damage to the heart muscle.

In following a series of cases of rheumatic fever in which frequent electrocardiograms were made, the diagnostic importance of disturbances in auriculoventricular conduction became apparent. The present study covers a period of nine years. Most of the patients had arthritis; some were predominantly of the cardiac type. The records of all rheumatic patients showing prolonged auriculoventricular conduction or heart block (partial or complete), as shown in the files of the cardiographic laboratory, were critically analyzed. The P-R interval

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* From the Department of Medicine, College of Physicians and Surgeons of Columbia University, and the Presbyterian Hospital.

* Read at the meeting of the American Society for Clinical Investigation, Washington, D. C., April 30, 1928.

1. Parkinson, J.; Gosse, A. H., and Gunson, E. B.: The Heart and Its Rhythms in Acute Rheumatism, Quart. J. Med. **13**:363, 1919-1920. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **39**:1, 1924.

2. Gerhardt, D.: Ueber Rückbildung des Adams-Stokes'schen Symptomkomplexes, Deutsches Arch. f. klin. Med. **93**:485, 1908. Bramwell, B.: A Case of Heart Block with Fibrous Degeneration and Partial Obliteration of the Bundle of His, Brit. M. J. **1**:995, 1909. Butterfield, H. G.: Acute Carditis and Heart Block, Heart **3**:203, 1911-1912. Naish, A. E., and Kennedy, A. M.: Heart Block in Acute Rheumatic Carditis, Lancet **2**:1242, 1914.

3. Cowan, J.; Kennedy, A. M.; Patterson, A. R., and Teacher, J. H.: Two Cases of Acute Endocarditis, Quart. J. Med. **4**:35, 1910.

was considered prolonged if it exceeded 0.2 second. Cases in which digitalis or quinidine was given during the time of observation were excluded. Salicylates and drugs of the cinchophen group were given to most of the patients. Although it has been shown that salicylate in certain cases of prolonged conduction appears to exert an effect in shortening the P-R interval,[4] it is believed that this action did not materially modify the results of the analysis. Electrocardiograms were taken in most cases at least once a week during the stay in the hospital and often daily during the acute phases of the disease. Follow-up examinations at varying intervals were also made.

For purposes of comparison, all other cases showing disturbances in auriculoventricular conduction were similarly reviewed. It is fair to state that in the nonrheumatic patients, graphic records usually were

TABLE 1.—*Data in One Hundred and Forty-Five Cases Showing Disturbances in Auriculoventricular Conduction*

	Total Cases	Total Cases, per Cent	Long P-R	Incomplete Block	Complete Block	Long P-R and Block at Different Times
Rheumatic fever	78	53.8	76	6	0	4
Arteriosclerotic and hypertensive heart disease	42	28.9	29	5	8	0
Syphilitic heart disease	10	6.9	8	1	1	0
Nonhemolytic streptococcus endocarditis	3	2.1	3	0	0	0
Miscellaneous	12	8.3	11	1	1	1
Total	145	100.0	127	13	10	5

taken at less frequent intervals. When the criteria mentioned were employed, a total of 145 cases was found in all groups. Of these, 127 showed a prolonged P-R interval. The importance of the latter observation, as will be pointed out, should particularly be stressed.

ANALYSIS OF MATERIAL

In a comparison of the incidence of impaired auriculoventricular conduction in the various clinical conditions in which it was encountered, certain striking contrasts are at once apparent (table 1). More than half (53.8 per cent) of the cases were instances of rheumatic fever. Next in numerical importance was the group including patients with arteriosclerotic and hypertensive heart disease (28.9 per cent). These were considered together for convenience in discussion and because the borderline between them is often ill-defined. The syphilitic cases comprised 6.9 per cent of the total and the cases of nonhemolytic strepto-

4. Levy, R. L., and Turner, K. B.: Variations in Auriculoventricular Conduction Time in Rheumatic Carditis with Salicylate Therapy, Proc. Soc. Exper. Biol. & Med. **25**:64, 1927.

coccus endocarditis only 2.1 per cent. In the miscellaneous group, which formed 8.3 per cent of the cases, were the following: hyperthyroidism, one case; hypothyroidism, one; diphtheria, one; *Staphylococcus aureus* bacteremia, one; chronic nephritis, one; congenital heart disease, one; acute tonsillitis, three; unknown, two. The three cases of acute tonsillitis are worthy of special mention. In them, prolonged conduction was found during or shortly after the attack, without other signs of disease. It is possible that in these patients, early myocardial involvement, perhaps due to rheumatism, was detected in the graphic records. Further studies along these lines are in progress.

In rheumatic fever, prolonged auriculoventricular conduction is by far the most frequent disturbance, whereas in the arteriosclerotic-

TABLE 2.—*Relative Frequency of Prolonged Auriculoventricular Conduction (Without Block) in One Hundred and Twenty-Seven Cases*

	Total Cases	Per Cent
Rheumatic fever	76	59.9
Arteriosclerotic and hypertensive heart disease	29	22.8
Syphilitic heart disease	8	6.3
Nonhemolytic streptococcus endocarditis	3	2.3
Miscellaneous	11	8.7
Total	127	100.0

TABLE 3.—*Incidence of Prolonged Auriculoventricular Conduction in Rheumatic Fever in Four Hundred and Three Cases*

P-R prolonged		112 (27.8%)
No digitalis	60 (14.9%)	
Received digitalis	52 (12.9%)	

hypertensive group, partial or complete heart block is relatively more common. In the remaining groups, as in rheumatism, a prolonged P-R interval is the more frequent observation.

From a study of table 1, then, it is established that conduction disturbances in the heart are observed much more often in rheumatic fever than in any other condition, and that lengthening of the P-R interval is the most important of these disturbances. The latter point is further emphasized in table 2.

If prolongation of auriculoventricular conduction is found more frequently in rheumatism than in other diseases, in what proportion of rheumatic patients is this evidence of myocardial involvement present? Of 403 cases of rheumatic fever observed electrocardiographically, 112 (27.8 per cent) showed a long P-R interval (table 3). Fifty-two (12.9 per cent) of these patients received digitalis in amounts which, it appears likely, were insufficient to affect auriculoventricular conduction. Other figures on the incidence of impaired conduction in rheumatism are

available. Thus, 87 per cent of Swift's cases [5] showed an increase in P-R time or incomplete block. The higher incidence in this series is due in part to the use of a less rigid criterion for prolongation and in part to the fact that only patients with the more severe forms of rheumatism were admitted to the Rockefeller Hospital. The figure reported from Mt. Sinai Hospital, New York,[6] 27.6 per cent, is more nearly like our own. It is based on a similar criterion for prolongation (0.2 second or over) and probably represents the average incidence in a general medical service.

The figure for the incidence of prolonged auriculoventricular conduction in subacute bacterial endocarditis is based on a small number of cases. In twenty-three patients, a long P-R time was found in three (13 per cent). In Libman's series of sixty-one cases,[6] prolonged conduction was observed in 16 per cent. It is, of course, possible that in

TABLE 4.—*Sex and Age of One Hundred and Thirty Patients Showing Disturbances in Auriculoventricular Conduction*

	Total Cases	Male	Female	Age	
				Range	Average
Rheumatic fever	78	51	27	7-56	27.4
Arteriosclerotic and hypertensive heart disease	42	27	15	35-82	60.2
Syphilitic heart disease	10	8	2	32-55	49.0
Total	130	86	44		

some of these a mixed infection was present, i. e., bacterial and rheumatic.

The sex and age of patients with impaired auriculoventricular conduction are shown in table 4. In rheumatic, arteriosclerotic-hypertensive and syphilitic groups, males predominate. In the first two groups, the ratio is about 2:1. The average age in each group approximates that at which the various diseases are most frequently encountered—rheumatism in the young, syphilitic heart disease in middle age and vascular degeneration in advancing years.

A correlation of conduction disturbances with other changes in the form of the electrocardiogram has not been attempted. In the rheumatic cases, lengthening of auriculoventricular conduction has, in general, been accompanied by leukocytosis (i. e., a white cell count of more than 10,000). The average counts ranged around 14,000 to 15,000 white cells per cubic millimeter. This parallelism was to be

5. Swift, H. F.: Rheumatic Fever, Am. J. M. Sc. **170**:631, 1925.

6. Rothschild, M. A.; Sacks, B., and Libman, E.: The Disturbances of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, Am. Heart J. **2**:356, 1927.

anticipated, since both a long P-R interval and leukocytosis are signs of active infection in the heart muscle. In five cases showing prolonged conduction the white cell count was normal.

DIAGNOSTIC APPLICATIONS

Impaired Auriculoventricular Conduction as an Aid in Differential Diagnosis.—If, then, prolonged conduction is more frequent in rheumatic fever than in any other disease, and this group of patients is distinguished by age limitations, the following diagnostic aphorism may be formulated: a prolonged P-R interval or heart block occurring in a person under the age of 35, who is not syphilitic and who has not taken digitalis, affords presumptive evidence of the presence of rheumatic carditis. On rare occasions, the differentiation between rheumatism and subacute bacterial endocarditis may be difficult. Often, the diagnosis of the rheumatic nature of a cardiac disturbance can be made in the absence of the usual criteria. The following case illustrates this point:

A young married woman, aged 26, while climbing in Switzerland six weeks prior to her visit to one of us, noted palpitation and dyspnea. During the next few days, these symptoms recurred several times. Two weeks later, in London, she had acute tonsillitis. Four days before our examination, she arrived in New York, exhausted and with a temperature of 101 F. The leukocyte count was 15,000. Her physician suspected infection of a sinus, but because of the presence of tachycardia and an apical systolic murmur, requested a cardiac examination. Pain in the joints, chills or sweats had not occurred.

The heart was normal in size; the rate was 116 per minute at rest. A blowing, mitral systolic murmur was present. An electrocardiogram showed a P-R interval of 0.25 second, without other changes. A diagnosis was made of rheumatic carditis. Ten days later, severe, generalized arthritis developed, yielding promptly to medication with salicylate. Six weeks after the patient was first seen, the conduction time was 0.2 second. Tonsillectomy was done. The patient has been well for four years, and there is now no evidence of cardiac damage.

In rare instances, heart block may be the first sign of rheumatic fever, as in the patient reported by White.[7] Such a patient recently came under our observation:

A housewife, aged 42, was admitted to the hospital complaining of shortness of breath, which had been noted on exertion for six months and which was becoming progressively worse. For nine days she had been in bed, but without medication.

She had scarlet fever at the age of 27. During adult life she suffered from severe tonsillitis on four occasions, the last attack having occurred six months before admission to the hospital. There was no history of pain in the joints or chorea.

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7. White, P. D.: Acute Heart Block Occurring as the First Sign of Rheumatic Fever, Am. J. M. Sc. **152**:589, 1916.

Examination on admission showed an obese woman. The temperature was 100.4. The tonsils were moderately large and red. The heart was not enlarged. The rhythm was irregular. There was a systolic murmur over the entire precordium. The peripheral vessels were soft. The blood pressure was 122 systolic; 95, diastolic. The leukocyte count was 13,300. The Wassermann reaction on the blood was negative.

An electrocardiogram taken the following morning showed incomplete heart block, and based on this observation a diagnosis of rheumatic carditis was made. The temperature on this day rose to 101.2.

On the morning of the third day in the hospital, the ankles and wrists became painful, red and swollen. The temperature was 102. Medication with salicylate was begun in doses of 8 Gm. daily. There was prompt relief from the arthritis and a fall in temperature.

The administration of salicylate was continued. Seventeen days after admission, dropped beats were no longer present, although P-R (conduction) time was still 0.28 second. Four weeks after admission, normal conduction time (0.16 second) was recorded for the first time. Five days later, because the patient felt

TABLE 5.—*Persistence of Prolonged Auriculoventricular Conduction in One Hundred and Twenty-Seven Cases*

	Total Cases	Only One Record	Tempo-rary	Perma-nent*
Rheumatic fever	76	18	45	13
Arteriosclerotic and hypertensive heart disease	29	19	3	7
Syphilitic heart disease	8	6	1	1
Nonhemolytic streptococcus endocarditis	3	1	0	2
Miscellaneous	11	4	4	3
Total	127	48	53	26

* Permanent in the sense of denoting the period of observation. The duration of this period was, of course, variable.

well, she left the hospital against advice, still taking acetylsalicylic acid. One month later, she reported for follow-up examination. Conduction time was normal (0.17 second), and she did not have any complaints.

In this case, incomplete heart block gave the clue to the rheumatic etiology of the condition twenty-four hours before arthritis appeared. The block persisted for seventeen days and prolonged auriculoventricular conduction for another eleven days. The systolic murmur over the precordium was the only sign of possible valvular involvement.

Prolonged Conduction as Evidence of Persistent Cardiac Involvement.—Although often transitory during the acute stages of the disease, prolonged conduction may continue for months, long after the other manifestations of rheumatic fever have subsided. In the great majority of cases it tends eventually to return to within normal limits; in a few, prolongation is permanent, probably due to fibrotic changes in the region of the auriculoventricular node or bundle. In table 5, the persistence of prolonged auriculoventricular conduction is shown in the various disease groups. In the arteriosclerotic-hypertensive group, permanent changes in conduction are relatively frequent, and result in partial or complete heart block.

The following case illustrates the value of graphic records in the detection of persistent myocardial lesions in rheumatic fever:

A trained nurse, aged 50, had her first attack of rheumatic fever following tonsillitis, two months before admission to the hospital. The heart was slightly enlarged, and a mitral systolic murmur was audible. The P-R interval was 0.32 second. After the patient had been in bed for a week the temperature, pulse and joints were normal and remained so, except for a slight flare-up after tonsillectomy. This was performed seven weeks after admission. The conduction time remained long (from 0.35 to 0.21 second) during the four months the patient was in the hospital and for five months thereafter (nine months in all), during which period a regimen of rest was conscientiously carried out. At the end of this time the P-R interval was found to be 0.17 second, and the patient returned to work. She has been well and working steadily for the past three years. The heart is still a little enlarged. There is no evidence of valvular disease or myocardial insufficiency.

SUMMARY

1. Disturbances in auriculoventricular conduction are found more frequently in rheumatic fever than in any other disease. Delayed conduction, as evidenced by prolonged P-R time, is much more common than heart block. These disturbances are usually transitory.

2. In arteriosclerotic and hypertensive heart disease, impaired conduction is encountered next in order of frequency. In this group of cases, heart block is relatively more common. The disturbances in conduction tend to become permanent.

3. In rheumatic fever, as seen in a general medical service, about 27 per cent of the cases show prolonged auriculoventricular conduction. This condition is usually, though not invariably, accompanied by leukocytosis during the active stages of the disease.

4. A prolonged P-R interval or heart block occurring in a person under the age of 35, who is not syphilitic and who has not taken digitalis, affords presumptive evidence of the presence of rheumatic carditis. This sign is often useful in establishing the rheumatic nature of a cardiac disturbance, in the absence of other criteria.

5. Prolongation of auriculoventricular conduction may persist and give evidence of myocardial lesions in rheumatic fever long after the other clinical manifestations of the disease have subsided.

CULTURAL AND SEROLOGIC REACTIONS WITH GREEN-PRODUCING MICROCOCCI FROM MEASLES*

N. S. FERRY, M.D.
AND
ARLYLE NOBLE, A.B.
DETROIT

During the past few years several papers have appeared with definite detailed descriptions of green-producing micrococci, obtained from measles, which were considered more or less closely associated with the etiology of the disease. From these original descriptions, it is apparent that the organisms differ from one another in many respects, although the impression has been given and the statement made by several writers that they are similar.

The present study was undertaken in an attempt to arrive at some definite conclusion, if possible, in regard to the relationship of these organisms to one another, and to determine, if they differ, wherein their fundamental differences lie, for the ultimate purpose of determining their relationship to measles.

The first mention of a green-producing micrococcus found frequently associated with measles was in 1917, by Tunnicliff.[1] This organism was described by the author as a green-producing diplococcus that was isolated from the blood, throat and eyes in early cases of measles. "In smears from the original culture, the organism appears as a very small, round, sometimes flattened diplococcus or in short chains, sometimes as clumps of cocci of varying size." Tests for the production of toxin were not mentioned in this original article by Tunnicliff, but later,[2] it seems apparent, she was convinced that it was not a true toxin producer as evidenced by the following statement: "The skin reaction to the diplococcus found by me in measles has been studied with a view to obtaining light on its relation to measles. Berkefeld W filtrates of aerobic and anaerobic cultures, grown from twenty-four hours to six days in broth with and without ascites fluid, failed to produce any reaction." When she prepared killed broth culture antigens, containing the whole culture, she was able, at the same time, to produce skin reactions in a dilution of

* Submitted for publication, Aug. 16, 1928.
* From the Medical Research Laboratories, Parke, Davis and Company.
* Read before the American Association of Immunologists, Washington, D. C., May 1, 1928.

1. Tunnicliff, R.: The Cultivation of a Micrococcus from Blood in Pre-eruptive and Eruptive Stages of Measles, J. A. M. A. **68**:1028 (April 7) 1917.

2. Tunnicliff, R.: Further Studies on a Diplococcus in Measles: A Measles Skin Reaction, J. Infect. Dis. **37**:193 (Sept.) 1925.

1:40. This reaction, however, could not be attributed solely to the filtrate. The organisms themselves must have played a large part in the phenomenon; in fact, Tunnicliff herself spoke of this antigen in a later article [3] as an "intracellular toxin."

In March, 1926, Ferry and Fisher [4] described "a small Gram-positive aerobic green-producing streptococcus appearing both in pairs and in chains, which produces an extracellular or soluble toxin specific to measles." In June and December, 1927, this work was given more in detail by Ferry [5] and later experiments with the organism and its toxin and antitoxin were described. Measles toxin has been readily produced with this organism in broth with or without ascites fluid or blood, and typical specific skin reactions have been demonstrated in man following intradermal injections of 0.1 cc. doses of from 1:400 to 1:600 dilutions of this toxin. Horses have been immunized with this toxin, giving a specific antitoxin which possesses a definitely measurable potency. In a paper by Ferry and co-workers,[6] results were reported which showed the clinical response to this antitoxin among patients susceptible to measles in comparison to the response of similar patients to measles convalescent serum under the same conditions and on the same wards.

In May, 1926, Hibbard and Duval [7] found a "small Gram positive coccus which was noted in culture tubes that contained semisolid plasma or hydrocele fluid. The micro-organism occurred singly or in pairs and short chains. Subsequently a good growth of the coccus was obtained upon ordinary blood agar plants, and under aerobic conditions at 37 C. incubation. A comparative cultural study of the various isolations revealed their complete correspondence with one another and the coccus described by Tunnicliff." With 0.2 cc. of a 1:10 dilution of a broth filtrate of this organism, Musser [8] produced a characteristic skin reaction claimed to be indicative of a toxin. Just prior to this, Tunnicliff [3] also

3. Tunnicliff, R., and Taylor, R. E.: Skin Tests in Measles, J. A. M. A. **87**: 846 (Sept. 11) 1926.

4. Ferry, N. S., and Fisher, L. W.: Measles Toxin: Its Preparation and Application as a Skin Test, as an Immunizing Agent, and for the Production of an Antitoxin, J. A. M. A. **86**:932 (March 27) 1926.

5. Ferry, N. S.: Etiology of Measles, Am. J. Pub. Health **17**:565 (June) 1927; Studies on the Etiology of Measles, Cincinnati J. M. **8**:191 (June) 1927; Recent Experimental Work on the Etiology of Measles, Nation's Health **9**:51 (Dec.) 1927.

6. Ferry, N. S.; Gordon, E. J.; Munro, F. W.; Steele, A. H., and Fisher, L. W.: Clinical Results with Measles Toxin and Antitoxin, J. A. M. A. **91**:1277 (Oct. 27) 1928.

7. Hibbard, R. J., and Duval, O. W.: Studies Upon the Virus of Measles, Proc. Soc. Exper. Biol. & Med. **23**:853 (June) 1926.

8. Musser, J. H.: Studies on Immunity to Measles, Proc. Soc. Exper. Biol. & Med. **24**:518 (March) 1927.

produced a skin reaction with a 1:10 dilution of a broth filtrate prepared from diplococcus. In this respect, the organisms of Hibbard and Duval and of Tunnicliff are similar in that they produce a filtrate which stimulated a skin reaction in a dilution of 1:10.

In May, 1927, Park, Williams and Wilson,[9] in a paper in which they attempted to determine the relation of the Tunnicliff and Ferry organisms to measles, described several different green-producing micrococci which they had obtained from measles, among which were some similar to the Tunnicliff diplococcus and some similar to the Ferry streptococcus. In regard to the production of toxin these authors stated, relative to the Ferry and Tunnicliff organisms, "in our hands both cultures make a toxin, but that from Ferry's culture is much stronger."

In October, 1927, Cary and Day[10] described a green-producing aerobic gram-positive diplococcus which seemed to be differentiated from other ordinary green producers by its reaction on salicin.

The work here presented is based on a study of the cultural and serologic relationship between the various strains of green-producing micrococci isolated from cases of measles and between these and similar micrococci from other sources. The organisms examined were: Four cultures furnished by Dr. Tunnicliff, blood 1, throat 2, nose 3 and sputum 7; three cultures from Dr. Duval, numbers 1, 2 and 3; one from Dr. Cary, number 47; two from Dr. Park, R 83 and "Tunnicliff"; four Ferry, 01860, 01933, 01934 and 01935, and six nonmeasles cultures, 01873 (endocarditis), 01885 (blood culture, infected glands), 01890 (Vincent's disease of the gums), 01966 (acute tonsilitis), 01983 (pyorrhea) and 01987 (acute endocarditis).

With these organisms the following reactions were studied: (1) morphologic and cultural reactions on various mediums; (2) cross-agglutination, agglutinin absorption and complement-fixation reactions with rabbit immune serums, and (3) agglutination, agglutinin absorption and complement-fixation reactions with measles convalescent serums.

MORPHOLOGIC AND CULTURAL REACTIONS

The morphologic and cultural characteristics of fourteen so-called measles cultures, isolated by various workers, are summarized in table 1.

For morphologic study, the organisms were grown for eighteen hours on whole blood agar (defibrinated rabbit blood, 0.2 per cent dextrose, p_H 7.6) and in broth (fresh veal infusion broth, 1 per cent Witte's peptone, 0.5 per cent sodium chloride, 0.1 per cent dextrose, p_H 8). Smears

9. Park, W. H.; Williams, A. W., and Wilson, M.: The Relation of the Tunnicliff and Ferry Diplococci to Measles, Am. J. Pub. Health **17**:460 (May) 1927.

10. Cary, W. E., and Day, T. A.: The Etiology of Measles, J. A. M. A. **89**: 1206 (Oct. 8) 1927.

TABLE 1.—*Morphology and Cultural Reactions of Green-Producing Micrococci from Measles*

Carbohydrates—Holman's Mediums

TABLE I.—*Morphology and Cultural Reactions of Green-Producing Micrococci from Measles*

	Morphology		Growth on			Carbohydrates—Holman's Mediums					
	Blood Agar	Broth	Blood Agar	Broth	Litmus Milk	Lactose	Mannit	Salicin	Saccharose	Inulin	Control
Ferry 01860, 01933, 01934, 01935	Gram-positive coccus; small, in pairs and short chains; in water of condensation, longer chains	Majority of organisms in chains (4-40)	Small, smooth colony with wide green zone	Uniform cloud	Marked acid.....16 hrs. Coagulation....48 hrs. ⅔ reduced..... 3 da. Color returns...10-14 da.	Marked acid 16 hrs.	Negative	Negative	Marked acid 16 hrs.	Negative	Negative
Cary 47.....	Same as Ferry	Majority of organisms in chains (4-40)	Small, smooth colony with wide green zone	Uniform cloud	Marked acid.....16 hrs. Coagulation....48 hrs. ⅔ reduced..... 3 da. Color returns...10-14 da.	Marked acid 16 hrs.	Negative	Negative	Marked acid 16 hrs.	Negative	Negative
Park 83.....	Gram-positive coccus; medium size, pairs and short chains; in moisture, longer chains, much variation in size	Long chains	Small, smooth colony; green	Uniform cloud	Acid.....24 hrs. Acid and coagulation.....48 hrs. Partial reduction..... 3 da.	Acid	Negative	Acid	Acid	Negative	Negative
Park-Tunnicliff...	Gram-positive coccus; small with pointed ends; in pairs and short chains; in moisture, much variation in size and shape, few short chains	Pairs and short chains	Small, smooth colony; green	Uniform cloud	Same as Park 83	Acid	Negative	Acid	Acid	Negative	Negative
Tunnicliff Blood 1..... .	Gram-positive coccus; medium size, single and in groups, no chains	Definitely in pairs, no chains	Large colony smooth, white; no change in blood	Uniform cloud with stringy sediment	Slight acid.....24 hrs. No coagulation. 2 wks.	Acid	Negative	Acid	Acid	Negative	Negative
Throat 2.....	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Uniform cloud	Marked acid and coagulation...24 hrs. Reduction.....48 hrs. Color returns... 5 da.	Acid	Negative	Acid	Acid	Negative	Negative
Nose 3.....	Gram-positive coccus; small, in short chains or pairs	Very small, in clumps	Rough colony with wide, green zone	Clear with flakey sediment	Marked acid and coagulation...24 hrs. Reduction..... 5 da.	Acid	Negative	Acid	Acid	Marked acid 16 hrs.	Negative
Sputum 7.....	Gram-positive coccus; small, in pairs and chains of pairs, long chains in moisture of condensation	Very long chains	Large, smooth colony with wide green zone	Slight cloud with heavy stringy sediment	Slight acid.....24 hrs. Acid and beginning coagulation... 5 da.	Negative	Negative	Negative	Acid	Negative	Negative
Hibbard and Duval 1.....	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Uniform cloud	Acid.....24 hrs. Coagulation and reduction..... 5 da.	Acid	Negative	Acid	Acid	Negative	Negative
Hibbard and Duval 2.....	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Uniform cloud	Marked acid and coagulation...16 hrs. Reduction.....48 hrs. Color returns... 5 da.	Acid	Negative	Acid	Acid	Negative	Negative
Hibbard and Duval 3.....	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Same as Park-Tunnicliff	Uniform cloud	Same as Hibbard and Duval 2	Acid	Negative	Acid	Acid	Negative	Negative

were made from the slant and from the moisture of condensation of the blood agar cultures, and from the broth, and stained by Gram's method.

For carbohydrate fermentation, a modification of Holman's serum broth medium was employed. Horse serum was substituted for cow serum and sugar-free broth was used. As a control, each organism was grown in the same medium to which no sugar was added.

Summary of Morphologic and Cultural Reactions.—The four Ferry cultures, *Streptococci morbilli,* are alike morphologically and culturally. They are small gram-positive streptococci, occurring in pairs and chains of pairs. They produce a small, smooth colony with a wide green zone on whole blood agar, grow in a uniform cloud in veal broth and are markedly acid with prompt coagulation and reduction in litmus milk. They ferment lactose and saccharose and are negative in mannit, salicin and inulin.

Cary 47 gives the same reactions as the Ferry cultures.

The two cultures from Park (R 83 and "Tunnicliff") are alike culturally but differ slightly morphologically, and are different from the Ferry cultures in morphology and in their fermentation of salicin.

No two of the cultures received from Tunnicliff give the same reactions. Throat 2 alone reacts similarly to Park-"Tunnicliff" and to the Hibbard and Duval cultures.

The three Hibbard and Duval cultures are much alike and agree with the Park-"Tunnicliff" and Tunnicliff-throat 2, but not with the Ferry or Cary cultures.

In addition, the bile solubility and hemolysin tests are both negative in all cultures.

CROSS-AGGLUTINATION REACTIONS WITH RABBIT IMMUNE SERUM

For the purpose of obtaining antiserums for making serologic tests, rabbits were treated [11] with four Ferry cultures (01860, 01933, 01934, 01935), two nonmeasles cultures (streptococcus, nonhemolytic, 01885 and 01873), and the two cultures received from Park (83 and "Tunnicliff").

Production of Antiserum.—In general, the method used was that given by Tunnicliff [12] for immunizing rabbits to the scarlatina streptococcus. She emphasized the necessity of immunizing with few and small doses to avoid polyvalency. For the first dose she used the sediment from 10 cc. of a twenty-four hour growth in ascites dextrose broth, suspended in saline and killed by heat. This was given intravenously, and after an interval of two weeks small numbers of living cocci (⅛ blood

11. A single strain was given to each rabbit.

12. Tunnicliff, R.: The Identification of the Streptococcus of Scarlet Fever, J. A. M. A. **87**:625 (Aug. 28) 1926.

agar slant) were injected intravenously every week or two to keep up the production of antibodies.

Two rabbits each were treated with the eight cultures after tests for agglutinins were made against *Bacillus bronchisepticus*, one measles strain, 01860, and one nonmeasles streptococcus, 01873. No rabbit was used whose serum showed any degree of agglutination to these organisms in amounts less than 0.05 cc., corresponding to a dilution of 1 : 20.

The first dose was composed of the entire sediment from 10 cc. of an eighteen hour broth culture (0.2 per cent dextrose, Witte's peptone, p_H 7.6), suspended in saline and killed by heating for thirty minutes at 56 C. The second dose, given nine days later, was 1/10 of a blood agar culture, and the third dose was 2/10 of a blood agar culture, ten days after the second dose. All injections were made intravenously.

The rabbits were sample bled and tested for agglutinins from six to eight days after each injection. The sixth day after the third injection one rabbit out of each group was bled to death. The remaining rabbits received four further doses of ½, 1, 2 and 3 blood agar cultures, five days apart, and were bled to death five days after the last injection. The serums were preserved with 0.2 per cent tricresol and stored at from 6 to 8 C.

There appeared to be little difference in the serums, the rabbits receiving the more injections in general produced serum of higher titer, but crossing was relatively the same.

Agglutination Experiments.—Cross-agglutination tests were made with the eight measles and nonmeasles cultures used for the immunization of rabbits. One culture from Cary, three from Tunnicliff and three from Hibbard and Duval have been tested for agglutinins against antiserums for Ferry and Park-"Tunnicliff" cultures. One of the cultures from Tunnicliff, nose 3, which produced a rough colony from the first, did not lend itself to agglutination. Four additional cultures of green-producing streptococci from sources other than measles were tested against anti-Ferry serum. The results of the latter experiments are taken up under agglutinin absorption experiments.

Preparation of Suspensions.—Suspensions were prepared from the sediment from broth cultures emulsified in phosphate broth and formaldehyde. Each culture was transferred daily for several generations in veal broth (0.1 per cent dextrose, p_H 8), and an eight hour growth inoculated into a flask of the same broth, incubated for from sixteen to eighteen hours, centrifugalized, and the sediment taken up in phosphate broth (1 per cent Witte's peptone, 1 per cent disodium phosphate, 0.5 per cent dextrose, p_H 8) plus 0.5 per cent formaldehyde.

Suspensions for agglutination tests were diluted with phosphate broth and formaldehyde to a density corresponding to five times that of a sus-

pension of *Bacillus typhosus* containing 2,000 million organisms per cubic centimeter.

Tests.—Agglutination tests were made by a rapid method developed by one of us[13] (A.N.): 0.1 cc. of heavy suspension plus 0.1 cc. of diluted serum, in small test tubes, shaken slowly for two minutes, 0.5 cc. of saline added and the results read.

A number of tests were made using both the rapid and a standard eighteen hour method (0.5 cc. of suspension plus 0.5 cc. of diluted serum, in small pointed tubes, incubated eighteen hours). Suspensions for the rapid method are five times as heavy and the serum dilutions are five times as concentrated as for the slow method. The results checked so closely that thereafter all tests were made by the rapid method only.

TABLE 2.—*Agglutination Results with Measles and Nonmeasles Streptococci*

		Highest Dilution of Serum Showing Definite Agglutination Against					
		Streptococcus morbilli				Streptococcus (Nonmeasles)	
Antiserum for		01860	01933	01934	01935	01873	01885
Streptococcus morbilli							
01860	Rabbit 1	**1:2,000**	1:2,000	1:2,000	1:2,000	1:2,000	1:2,500
	2	**1:2,000**	1:2,500	1:2,500	1:2,500	1:5,000	1:2,000
01933	Rabbit 3	1:2,500	**1:2,500**	1:2,500	1:5,000	1:2,500	1:2,500
	4	1:2,000	**1:1,000**	1:2,500	1:2,500	1:5,000	1:1,000
01934	Rabbit 5	1:1,000	1:1,000	**1:2,000**	1:1,000	1:2,500	1:2,000
	6	1:2,500	1:2,500	**1:5,000**	1:5,000	1:5,000	1:5,000
01935	Rabbit 9	1:2,500	1:2,000	1:2,500	**1:2,500**	1:5,000	1:5,000
	10	1:2,000	1:2,000	1:2,500	**1:2,500**	1:2,500	1:2,500
Streptococcus (nonmeasles)							
01873	Rabbit 15	1:2,000	1:2,500	1:2,500	1:2,500	**1:10,000**	1:2,500
	16	1:500	1:500	1:1,000	1:1,000	**1:2,000**	1:500
01885	Rabbit 17	1:2,000	1:1,000	1:2,000	1:2,500	1:10,000	**1:10,000**
	18	1:500	1:500	1:1,000	1:1,000	1:2,000	**1:2,500**

Table 2 shows the results of cross-agglutination tests between *Streptococcus morbilli* and two nonmeasles streptococci; table 3 gives the results with thirteen green-producing micrococci from measles, isolated by various investigators.

Summary of Agglutination Experiments.—1. Serums of high agglutinin titer were produced in rabbits by three and seven injections respectively of micrococci from measles and nonmeasles cases.

2. These serums, preserved with cresol and stored in the icebox, have retained their agglutinin titers for more than one year.

3. The four *Streptococcus morbilli* strains and the two nonmeasles cultures gave complete cross-agglutination reactions.

4. Cary 47 was agglutinated by anti-Ferry serum but not by anti-Park-"Tunnicliff" serum.

13. Noble, A.: A Rapid Method for the Macroscopic Agglutination Test, J. Bact. **14**:287 (Nov.) 1927.

TABLE 3.—*Agglutination Results with Green-Producing Micrococci from Measles*

Antiserum for		Highest Dilution of Serum Showing Definite Agglutination Against												
		Ferry				Cary	Park		Tunnicliff			Hibbard and Duval		
		01860	01933	01934	01935	47	83	Tunnicliff	Blood 1	Throat 2	Sputum 7	1	2	3
Ferry	01860	1:2,000	1:2,000	1:2,000	1:2,000	1:2,400	—	—	—	—	—	—	—	—
	01933	1:2,500	1:2,500	1:2,500	1:5,000	1:2,500	—	—						
	01934	1:1,000	1:1,000	1:2,000	1:1,000	..	—	—						
	01935	1:2,500	1:2,000	1:2,500	1:2,500	..	—	—						
Park	83	—	—	—	—	..	1:5,000	1:5,000						
Park-Tunnicliff		—	—	—	—	—	1:5,000	1:5,000	1:200	1:200	1:2,400	1:2,400	1:2,400	1:2,400

5. Park 83 and Park-"Tunnicliff" cross agglutinated but did not agglutinate against Ferry serum.

6. The Tunnicliff and Hibbard and Duval cultures were positive against Park-"Tunnicliff" serum and negative to Ferry serum.

AGGLUTININ ABSORPTION REACTIONS WITH RABBIT IMMUNE SERUM

Agglutinin absorption experiments were made with the same antiserums and cultures as those used for agglutination. Each serum was absorbed with its homologous culture and with heterologous cultures, when agglutinable, and agglutination tests were made on the resulting absorbed serums.

Suspensions for Absorption.—These were prepared from the same emulsions as suspensions for agglutination, as follows: on the day a test was to be made, a suspension was centrifugalized at high speed for

TABLE 4.—*Serum Dilutions*

			0.1 cc.
A.	1:5	— absorbed serum	= 1:50
B.	1:10	— 0.4 cc. A + 0.4 cc. saline	= 1:100
C.	1:20	— 0.2 cc. A + 0.6 cc. saline	= 1:200
D.	1:40	— 0.1 cc. A + 0.7 cc. saline	= 1:400
E.	1:80	— 0.1 cc. B + 0.7 cc. saline	= 1:800
F.	1:100	— 0.1 cc. B + 0.9 cc. saline	= 1:1,000
G.	1:200	— 0.1 cc. D + 0.4 cc. saline	= 1:2,000
H.	1:240	— 0.1 cc. D + 0.5 cc. saline	= 1:2,400
I.	1:500	— 0.1 cc. F + 0.4 cc. saline	= 1:5,000
J.	1:1,000	— 0.1 cc. F + 0.9 cc. saline	= 1:10,000

a long period (from twenty to thirty minutes) and a 50 per cent suspension of the packed cells made in saline.

The Absorptions.—Absorptions were also made by the rapid method: one part suspension (50 per cent cells) plus one part undiluted serum plus three parts saline, making approximately a 1:5 dilution of serum.

To a centrifuge tube (5.5 by 1.5 cm.) was added 0.3 cc. of suspension, 0.3 cc. of serum and 0.9 cc. of saline. The tube containing the mixture was placed in a rack, the rack inclined until the tube was almost horizontal and it was then shaken slowly for ten minutes. It was centrifugalized for ten minutes, the resulting clear fluid drawn off by pipet and dilutions made as shown in table 4.

Unabsorbed serum was diluted 1:5 and the same dilutions made of it. When more than 1.2 cc. of absorbed serum was needed, two tubes of the suspension-serum-saline mixture were made, as more than 1.5 cc. in this size centrifuge tube does not allow for thorough mixing. The agglutination tests were carried out as before.

Table 5 gives the results of a single agglutinin absorption experiment with an antiserum for *Streptococcus morbilli*. The unabsorbed and

absorbed serum dilutions were made at the same time and in parallel. When an antistreptococcus morbilli serum was absorbed by its homologous strain, agglutinins for both the measles and nonmeasles cultures were removed. When the same serum was absorbed by a nonmeasles streptococcus, which it agglutinated, the agglutinins for that culture were removed while the measles agglutinins were but slightly reduced.

Table 6 is a summary of the agglutinin absorption results with the four strains of *Streptococcus morbilli* and two nonmeasles streptococci; table 7 gives the agglutination and agglutinin absorption results with four additional nonmeasles streptococci which culturally are identical

TABLE 5.—*Agglutinin Absorption Experiment with an Antistreptococcus Morbilli Serum*

Antiserum for S. morbilli 01860 Rabbit 2	Agglutination*								
	1:50	1:100	1:200	1:400	1:800	1:1,000	1:2,000	1:2,400	Control
Before absorption against S. morbilli									
01860.....	++++	++++	++++	++++	++++	+++	+	—	—
01933.....	++++	++++	++++	++++	++++	++++	+	—	—
01934.....	++++	++++	++++	++++	+++	++	—	—	—
01935.....	++++	++++	++++	++++	++++	++++	+	—	—
Streptococcus (nonmeasles) 01873....	++++	++++	++++	++++	++++	++++	—	—	—
01885....	++++	++++	++++	++++	++++	+++	—	—	—
Absorbed by S. morbilli 01860 against 01860.....	—	—	—	—					
01933.....	—	—	—	—					
01934.....	—	—	—	—					
01935.....	—	—	—	—					
01873.....	—	—	—	—					
01885.....	—	—	—	—					
Absorbed by Streptococcus (nonmeasles) 01885 against 01860.....	++++	++++	++	—	—	—	—	—	
01933.....	++++	++++	—	—	—	—	—	—	
01934.....	++++	++++	++	+	—	—	—	—	
01935.....	++++	++++	++	+	—	—	—	—	
01873.....	++++	++++	++++	+++	+	—	—	—	
01885.....	—	—	—	—					

* ++++, +++, ++, + and — mean complete, marked, partial, slight and no agglutination.

with *Streptococcus morbilli*. Table 8 gives the results with the green-producing micrococci from various workers.

Summary of Agglutinin Absorption Experiments.—1. When a serum produced by injecting *Streptococcus morbilli* was absorbed by that culture, both specific and group agglutinins were removed (tables 5 and 6).

2. When the same serum was absorbed by a nonmeasles streptococcus, the agglutinins for that culture, group agglutinins, were removed, while the measles agglutinins, specific, were only slightly reduced (tables 5, 6 and 7).

3. The four *Streptococcus morbilli* strains appeared to be similar by agglutinin absorption.

(*a*) When an antiserum for 01860 was absorbed by 01933, 01934 or 01935, the agglutinins for 01860 were greatly reduced.

TABLE 6.—*Agglutinin Absorption Results with Measles and Nonmeasles Streptococci*

Antiserum for	Highest Dilution of Serum Showing Definite Agglutination Against: Streptococcus morbilli 01860	01933	01934	01935	Streptococcus (Nonmeasles) 01873	01885
S. morbilli 01860 Rabbit 1						
Before absorption	**1:2,000**	1:2,000	..	1:2,000	**1:2,400**	1:2,000
Absorbed by S. morbilli 01860	—	—	..	—	—	—
S. (nonmeasles) 01873	1:1,000	1:400	..	1:1,000	—	1:800
Rabbit 2						
Before absorption	**1:2,000**	1:2,000	1:1,000	1:2,000	1:1,000	1:1,000
Absorbed by S. morbilli 01860	—	—	—	—	—	—
01933	—	—	—	—		
01934	—	—	—	—		
01935	1:100	1:100	1:100	1:100		
S. (nonmeasles) 01885	1:200	1:100	1:400	1:400	1:800	—
S. morbilli 01933 Rabbit 3						
Before absorption	**1:2,400**	**1:2,400**	1:2,400	1:2,400	**1:2,400**	1:2,400
Absorbed by S. morbilli 01933	—	—	..	..	—	—
01860	1:200	1:400	1:400	1:400		
S. (nonmeasles) 01885	1:1,000	1:1,000	..	..	1:400	—
Rabbit 4						
Before absorption	1:2,000	**1:2,000**	..	..	1:5,000	1:1,000
Absorbed by S. morbilli 01933	—	—	..	..	—	—
S. (nonmeasles) 01885	1:1,000	1:1,000	..	..	1:400	—
S. morbilli 01934 Rabbit 5						
Before absorption	1:1,000	..	**1:2,000**	..	1:2,400	1:1,000
Absorbed by S. morbilli 01934	—	..	—	..	—	—
S. (nonmeasles) 01885	1:200	..	1:400	..	1:400	—
Rabbit 6						
Before absorption	1:5,000	1:5,000	**1:5,000**	1:5,000	1:5,000	1:5,000
Absorbed by S. morbilli 01934	—	..	—	..	—	—
01860	—	1:100	1:100	**1:100**		
S. (nonmeasles) 01885	1:1,000	..	1:2,000	..	1:2,000	—
S. morbilli 01935 Rabbit 9						
Before absorption	1:2,400	1:2,400	1:2,400	**1:2400**	1:5,000	1:5,000
Absorbed by S. morbilli 01935	—	..	..	—	1:50	—
01860	—	—	1:50	1:50		
S. (nonmeasles) 01885	1:800	..	..	1:1,000	1:2,000	—
Rabbit 10						
Before absorption	**1:2,000**	..	..	**1:2,400**	1:2,400	1:2,400
Absorbed by S. morbilli 01935	—	..	..	—	1:50	—
S. (nonmeasles) 01885	1:400	..	..	1:400	1:400	—
S. (nonmeasles) 01873 Rabbit 15						
Before absorption	1:800	1:2,400	..	..	**1:10,000**	1:2,000
Absorbed by S. (nonmeasles) 01873	—	—	..	..	1:50	—
S. morbilli 01860	—	—	..	..	1:1,000	1:100
Rabbit 16						
Before absorption	1:200	1:400	..	..	**1:2,000**	1:400
Absorbed by S. (nonmeasles) 01873	—	—	..	..	—	—
S. morbilli 01860	—	—	..	..	1:200	—
S. (nonmeasles) 01885 Rabbit 17						
Before absorption	1:2,500	1:1,000	1:2,000	1:2,400	1:5,000	**1:10,000**
Absorbed by S. (nonmeasles) 01885	1:100	—	—	—	1:50	1:200
S. morbilli 01860	1:50	—	—	1:100	1:400	1:1,000
Rabbit 18						
Before absorption	**1:800**	1:1,000	1:1,000	1:1,000	1:2,000	**1:2,400**
Absorbed by S. (nonmeasles) 01885	—	—	—	—	—	—
S. morbilli 01860	—	—	—	—	—	1:1,000

(*b*) And, conversely, when an antiserum for 01933, 01934, or 01935 was absorbed by 01860, the agglutinins for 01933, 01934 and 01935 were greatly reduced (table 6).

(*c*) Also, the agglutinins for all were absorbed from an antistreptococcus morbilli serum by any one strain of *Streptococcus morbilli*.

4. Two nonmeasles cultures of green-producing streptococci, 01873 and 01885, while agglutinating antiserum for *Streptococcus morbilli* to titer, were distinguished from *Streptococcus morbilli* by absorption.

(*a*) When an antiserum for *Streptococcus morbilli* was absorbed with nonmeasles streptococcus, the agglutinins for *Streptococcus morbilli* were only slightly reduced (tables 5 and 6).

TABLE 7.—*Agglutination and Agglutinin Absorption Results with Nonmeasles Streptococci*

Antiserum for S. morbilli 01860 Rabbit 2	Agglutination							
	1:50	1:100	1:200	1:400	1:800	1:1,000	1:2,000	Controls
Before absorption against S. morbilli 01860	++++	++++	++++	++++	++++	+++	+	—
Streptococcus (nonmeasles) 01890	—	—	—	—	—	—	—	—
01966	++++	++++	++++	+++	++	+	—	—
01983	++++	++++	++++	+++	—	—	—	—
01987	++++	++++	++++	+++	—	—	—	—
Absorbed by 01966 Against 01966	—	—	—	—				
01860	++++	++++	++++	+++	+	—	—	
Absorbed by 01983 Against 01983	—	—	—	—				
01860	++++	++++	++++	++++	++	+	—	
Absorbed by 01987 Against 01987	—	—	—	—				
01860	++++	++++	++++	++++	+++	+	—	

(*b*) And, conversely, when an antiserum for a nonmeasles culture was absorbed with *Streptococcus morbilli*, the agglutinins for the nonmeasles culture were only slightly reduced (table 6).

5. Three nonmeasles cultures, 01966, 01983 and 01987, are presumptively different from *Streptococcus morbilli* as no one of them absorbs agglutinins for 01860 from an 01860 serum (table 7).

6. Cary 47 and the Ferry cultures are presumptively similar. When a Ferry serum was absorbed by Cary 47, the agglutinins for each culture were removed (table 8).

7. The two cultures received from Park appear to be similar (table 8).

(*a*) When an antiserum for Park 83 was absorbed by Park-"Tunnicliff," agglutinins for Park 83 were greatly reduced.

(*b*) And, conversely, when an antiserum for Park-"Tunnicliff" was absorbed by Park 83, agglutinins for Park-"Tunnicliff" were greatly reduced.

TABLE 8.—*Agglutinin Absorption Results with Green-Producing Micrococci from Measles*

Antiserum for	Highest Dilution of Serum Showing Definite Agglutination Against												
	Ferry				Cary	Park		Tunnicliff			Hibbard and Duval		
	01860	01933	01934	01935	47	83	Tunnicliff	Blood 1	Throat 2	Sputum 7	1	2	3
Ferry 01860													
Before absorption	**1:2,000**	1:1,000	1:2,000	1:2,000	1:2,400	—	—	—	—	—	—	—	—
Absorbed by Ferry 01860	—	—	—	—	—								
01933	—	—	—	—									
01934	—	—	—	—									
01935	1:100	1:100	1:100	1:100									
Cary 47	—	—	..	..	—								
Park 83													
Before absorption	—	—	—	—	..	**1:5,000**	1:5,000						
Absorbed by Park 83	..	..	..	..	..	—	—						
Park-Tunnicliff	..	..	..	..	..	1:100	—						
Park-Tunnicliff													
Before absorption	—	—	—	—	—	1:5,000	**1:5,000**	1:200	1:200	1:2,400	1:2,400	1:2,400	1:2,400
Absorbed by Park-Tunnicliff	..	..	..	..	..	—	—						
Park 83	..	..	..	..	..	—	1:100						
Tunnicliff, blood 1	..	..	..	..	..	..	1:5,000	—					
Tunnicliff, throat 2	..	..	..	..	..	..	—	..	—				
Tunnicliff, sputum 7	..	..	..	..	..	..	1:2,400	..	..	—			
Duval 3	..	..	..	..	..	..	—	..	..	..	—	—	—

8. Tunnicliff-throat 2 is presumptively similar to Park-"Tunnicliff," as it absorbed agglutinins for that culture (table 8).

9. Tunnicliff-blood 1 and sputum 2, while agglutinating in Park-"Tunnicliff" serum, did not absorb agglutinin for Park-"Tunnicliff."

10. The three Hibbard and Duval cultures are presumptively alike and similar to Park-"Tunnicliff." When Park-"Tunnicliff" serum was absorbed by Hibbard and Duval 3, agglutinins for Hibbard and Duval 1, 2 and 3 and for Park-"Tunnicliff" were greatly reduced (table 8).

COMPLEMENT-FIXATION REACTIONS WITH RABBIT IMMUNE SERUM

Homologous and cross-complement-fixation tests were made with the same serums and cultures as those used for agglutination.

Preparation of Antigens for Complement-Fixation Tests.—Antigens were prepared by a modification of the Wilson and McNeil method for defatted gonococcus antigens.[14]

Each culture was grown for twenty-four hours on 0.2 per cent dextrose-ascitic agar in Roux flasks of 1 quart capacity; the growth washed off in 15 cc. of saline and made up to 50 cc. per flask. Each suspension was shaken for fifteen minutes in a mechanical shaker, then centrifugalized and the supernatant fluid poured off.

To the sediment from ten flasks in a centrifuge tube was added 50 cc. of absolute alcohol. This mixture was heated in a water-bath at 56 C. for thirty minutes, and was stirred constantly with a glass rod. It was then centrifugalized for ten minutes and the alcohol discarded. To the residue, 50 cc. of Squibb's ether was added and stirred constantly for thirty minutes at room temperature, again centrifugalized, the ether discarded and the sediment allowed to dry at room temperature. When thoroughly dry and free from the odor of ether, the powder was triturated in distilled water plus 0.5 per cent of phenol in the proportion of 1 Gm. in 200 cc. These bacterial suspensions were then autoclaved for twenty minutes at a pressure of 15 pounds.

Satisfactory and stable antigens of the sixteen cultures have been prepared by this method. They are not hemolytic in doses of 0.5 cc. of a 1:5 dilution, but they are slightly anticomplementary, and the antigenic units range from 0.5 cc. of 1:100 to 0.5 cc. of 1:1,000.

The Test.—The complement-fixation tests were made by an adaptation of the new Kolmer method [15] for syphilis.

Amboceptor and complement were titrated daily. Four units of antigen (01860) were used in the complement titration. The serum from

14. Park, W. H., and Williams, A. W.: Pathogenic Microörganisms, ed. 8, Philadelphia, Lea & Febiger, 1924, pp. 258 and 273.

15. Kolmer, J. A.: Infection, Immunity and Biologic Therapy, ed. 3, Philadelphia, W. B. Saunders Company, 1924, p. 478.

not less than three guinea-pigs was pooled for complement. The fixation period was eighteen hours at from 6 to 8 C.

The dose of antigen was from two to four times the antigenic unit, in most cases four times, depending on the anticomplementary unit. Antigens, for which we had no homologous antiserum, were used in doses of one-fourth the anticomplementary unit.

The serum dilutions were from 1:20 to 1:1,250 The dose was 0.5 cc. of these, making the final dilutions 1:40 to 1:2,500, the same dilutions as used for the straight agglutination tests. A few of the serums were anticomplementary, but the serum from at least one rabbit on each organism could be utilized.

Tables 9 and 10 give the results of the complement-fixation tests.

Summary of the Complement-Fixation Experiments.—1. The four strains of *Streptococcus morbilli* and the two nonmeasles streptococci showed cross fixation to titer (table 9).

TABLE 9.—*Complement-Fixation Results with Measles and Nonmeasles Streptococci*

		Highest Dilution of Serum Showing Definite Fixation Against Antigens of					
		Streptococcus morbilli				Streptococcus (Nonmeasles)	
Antiserum for		01860	01933	01934	01935	01873	01885
Streptococcus morbilli							
01860	Rabbit 1	**1:1,000**	1:1,000	1:2,000	1:1,000	1:1,000	1:1,000
	Rabbit 2	**1:500**	1:500	1:1,000	1:400	1:500	1:500
01933	Rabbit 4	1:500	**1:400**	1:1,000	1:500	1:100	1:100
01934	Rabbit 5	1:1,000	1:1,000	**1:2,000**	1:1,000	1:500	1:500
01935	Rabbit 10	1:500	1:500	1:1,000	**1:500**	1:400	1:500
Streptococcus (nonmeasles)							
01873	Rabbit 15	1:2,500	1:2,500	1:2,500	1:2,500	**1:2,500**	1:2,500
01885	Rabbit 18	1:1,000	1:500	1:1,000	1:400	1:400	**1:500**

2. Ferry 01860 did not cross with Park 83 or Park-"Tunnicliff" serum (table 10).

3. Cary 47 showed marked fixation against antistreptococcus morbilli serum only.

4. Park 83, Park-"Tunnicliff," Tunnicliff-throat 2, and the three Hibbard and Duval cultures showed fixation with Park 83 and Park-"Tunnicliff" serum and were negative to Ferry serum.

5. Tunnicliff strains, blood 1, nose 3 and sputum 7 were negative to both Ferry and to Park-"Tunnicliff" serum.

AGGLUTINATION AND COMPLEMENT-FIXATION TESTS WITH MEASLES CONVALESCENT SERUM

The serum was furnished by Dr. Fred M. Meader of the Detroit Board of Health, from patients whose histories were verified by the physician who attended them during their attack of measles. All the serums

TABLE 10.—*Complement-Fixation Results with Green-Producing Micrococci from Measles*

Antiserum for	Highest Dilution of Serum Showing Definite Fixation Against Antigens of													
	Ferry				Cary	Park		Tunnicliff				Hibbard and Duval		
	01860	01933	01934	0.1935	47	83	Tunnicliff	Blood 1	Throat 2	Nose 3	Sputum 7	1	2	3
Ferry 01860	1:1,000	1:1,000	1:2,000	1:1,000	1:500	—	—	—	—	—	—	—	—	—
01933	1:500	1:400	1:1,000	1:500										
01934	1:1,000	1:1,000	1:2,000	1:1,000										
01935	1:500	1:500	1:1,000	1:500										
Park 83	1:40	.....	.....	.....	1:40	1:500	1:500	—	1:500	—	—	1:200	1:200	1:500
Park-Tunnicliff	1:80	.....	.....	.....	1:80	1:500	1:500	1:80	1:500	—	—	1:200	1:200	1:500

were preserved with tricresol and were filtered clear immediately before using. This serum was being employed by the Detroit Board of Health for prophylactic purposes. One hundred and fifty-one serums have been studied, but, as many of these were repeated bleedings, results with the first bleedings only are considered in this report.

Serums from eighty-three patients convalescent from measles were tested for agglutinins for Ferry 01860, Cary 47, Park-"Tunnicliff" and Hibbard and Duval 3, and thirty-nine were tested for complement-fixation against antigens of the same organisms. These four cultures were chosen because they seemed to be the most representative of the two predominating groups among the micrococci studied.

TABLE 11.—*Agglutination and Complement-Fixation Results with Measles Convalescent Serums* *

Serum Number	Age of Patient When Bled, Years	Time Since Patient Had Measles	Agglutination Reaction				Complement Fixation			
			Ferry 01860	Cary 47	Park-Tunnicliff	Hibbard and Duval	Ferry 01860	Cary 47	Park-Tunnicliff	Hibbard and Duval
2	27	5 mos.	4 3 3 2	4 4 3 -	—	—	A.C.†	.....	.....	.....
3	34	1½ mos.	3 4 4 2	4 4 4 4	1 - -	1 - -	A.C.	.....	.....	.....
4	28	2 mos.	4 3	4 4	—	....	3 2 1 -	2 1 1 -	—	2 1 - -
5	13	2½ mos.	3 1 - -	4 2 1 -	—	—	4 3 2 1	4 3 2 -	—	3 2 1 -
6	15	2½ yrs.	1 - - -	2 1 - -	—	—	A.C.	.....	.....	.....
7	26	1 mo.	4 3 2 1	4 3 - -	—	—	A.C.	.....	.....	.....
11	15	2 mos.	2 1 - -	2 1 - -	—	—	2 1 - -	2 1 - -	—	—
12	11	2 mos.	3 4 1 -	3 1 - -	—	2 1	A.C.	.....	.....	.....
14	19	2 mos.	3 1 - -	4 3 - -	—	2 - -	3 2	3 2	—	—
15	24	3 mos.	3 2 1 -	3 2 1 -	—	—	2 1 - -	2 1 - -	—	1 - - -
16	12	15 days	4 4 1 -	4 4 1 -	—	—	2 1 - -	2 1 - -	—	1 - -
17	22	3 mos.	—	—	—	—	A.C.	.....	.....	.....
19	21	11 mos.	4 2 1 -	4 3 - -	—	—	4 3 1 -	4 4 1 -	4 1 - -	4 3 - -
20	30	18 days	3 2 - -	4 4 4 -	—	—	3 1 - -	3 1 - -	1 - - -	2 - - -
21	17	10 mos.	3 2 1 -	2 1 - -	—	—	3 2 1 -	2 1 1 -	—	—
22	26	3 wks.	4 4 3 2	4 4 4 4	1 - -	—	A.C.	.....	.....	.....
28	23	2 mos.	2 1 - -	1 - - -	1 - -	—	1 1 - -	1 1 - -	—	—
33	23	2 yrs.	4 4 4 1	4 4 4 3	—	—	4 4	4 3	4 -	4 -
41	31	3½ yrs.	2 1 - -	3 3 1 -	—	4 - -	3 2 1 -	3 2 1 -	1 - - -	1 - - -
43	40	10 mos.	2 1 - -	2 1 - -	—	—	—	—	—	—
44	16	10 mos.	2 2 1 -	3 1 - -	—	—	—	—	—	—
49	14	1 mo.	—	1 - - -	—	—	—	—	—	—
51	13	1 mo.	—	4 3 - -	—	—	—	1 - - -	3 2 - -	2 1 - -
52	15	1-2 mos.	2 - - -	4 3 - -	—	—	1 - - -	1 - - -	—	—
53	28	1 yr.	—	—	—	—	1 - - -	1 - - -	—	—

* Serum amounts used in agglutination and complement fixation tests were: 0.1, 0.05, 0.025 and 0.01 cc. 4, 3, 2, 1, - mean the complete, marked, partial, slight and no agglutination, or complement fixation.
† A.C. = anticomplementary.

Agglutination tests were made by the rapid method, undiluted serum being used in amounts of 0.1, 0.05, 0.025 and 0.01 cc. delivered with a 0.1 or 0.2 cc. pipet to the bottom of the tubes. A preliminary reading was made immediately after the two minute shaking period and the addition of 0.5 cc. of saline, and the tests were allowed to stand at room temperature overnight, when the final reading was made. Reactions with serums of such low titer are easier to read after standing for a few hours.

Complement-fixation tests were made by the new Kolmer method; the same amounts of serum were used made up to 0.5 cc. with saline.

Table 11 gives the results with serum from the first twenty-five patients, on whom both tests were made, together with the age of the

patient and the length of time since the patient had measles. Table 12 gives a summary of the agglutination and complement-fixation results.

In addition to these, serums from sixteen patients who had had measles not more than two months prior to bleeding were tested for agglutinins against all thirteen measles cultures being studied.

Summary of Agglutination and Complement-Fixation Experiments.—Considering the eighty-three serums tested against the four cultures, 86.7 per cent agglutinated the Ferry culture, 90.3 per cent Cary 47, 8.4 per cent Park-"Tunnicliff" and 9.6 per cent the Hibbard and Duval culture 3. The Ferry and Cary cultures often showed marked agglutination in all four amounts, while the Park-"Tunnicliff" and Duval culture seldom showed more than 2+ agglutination in the largest amount (0.1 cc).

Of the convalescent serums on which complement-fixation tests were made, twelve were anticomplementary, and of the remaining twenty-

TABLE 12.—*Summary of Results with Measles Convalescent Serum*

	Agglutination				Complement Fixation			
	Total Tested	Reaction		Per Cent	Total Tested	Reaction		Per Cent
		+	—	+		+	—	+
Ferry 01860	83	72	11	86.7	27	21	6	78
Cary 47	83	75	8	90.3	27	21	6	78
Park-Tunnicliff	83	7	76	8.4	27	9	18	33
Hibbard and Duval 3	83	8	72	9.6	27	13	14	48

seven, 78 per cent showed fixation with both Ferry and Cary cultures, 33 per cent with Park-"Tunnicliff" and 48 per cent with the Duval culture.

Of the sixteen serums from recent cases tested against thirteen suspensions, all agglutinated the four Ferry strains and Cary 47. One serum was positive to all cultures. Thirteen were negative to Park-"Tunnicliff," Tunnicliff-throat 2 and the three Duval cultures. Nine were positive to Tunnicliff-blood 1 and fourteen were positive to Tunnicliff-sputum 7.

AGGLUTININ ABSORPTION REACTIONS WITH MEASLES CONVALESCENT SERUM

Owing to the fact that fourteen of the sixteen serums from recent cases of measles agglutinated Tunnicliff's culture sputum 7, it was decided to try absorption tests with such serums. As the nonmeasles culture 01885 crossed so completely with *Streptococcus morbilli* serum, this organism also was included.

A number of serums from recent cases were tested for agglutinins against these two cultures in addition to Ferry 01860, Cary 47, Park-

"Tunnicliff" and Duval 3, and the five serums giving the highest titers were selected for absorption reactions.

Each serum was absorbed by Ferry 01860, Tunnicliff-sputum 7 and streptococcus (nonhemolytic) 01885, and the resulting absorbed serums were tested for agglutinins against the same three suspensions and Cary 47.

For absorption, equal parts of serum and suspension (25 per cent packed cells) were shaken slowly in a centrifuge tube for ten minutes; centrifugalized for ten minutes and serum removed. The absorbed serum was considered as a dilution of 1:2, though actually it is not diluted that much because of the space occupied by the bacteria in the

TABLE 13.—*Agglutinin Absorption Experiment with a Convalescent Serum*

	Agglutination					
Convalescent Serum 146	1:10	1:20	1:40	1:80	1:100	Control
Before absorption against						
Ferry 01860	++++	++++	+++	++	+	—
Cary 47	++++	++++	+++	++	+	—
Park-Tunnicliff	—	—	—	—	—	—
Duval 3	—	—	—	—	—	—
Tunnicliff, sputum 7	++++	+++	—	—	—	—
Streptococcus 01885	++++	++++	++++	++++	+++	—
Absorbed by Ferry 01860 against						
Ferry 01860	—	—	—	—		
Cary 47	—	—	—	—		
Sputum 7	++	+	—	—		
Streptococcus 01885	++	+	—	—		
Absorbed by sputum 7 against						
Ferry 01860	+++	++	+	+		
Sputum 7	—	—	—	—		
Streptococcus 01885	++++	++++	++++	+++		
Absorbed by Streptococcus 01885 against						
Ferry 01860	++	+	+	±		
Cary 47	+++	++	++	+		
Sputum 7	++++	+++	—	—		
Streptococcus 01885	—	—	—	—		

25 per cent suspension. This error, however, is in the right direction as it makes the test for absorption that much more rigid.

The unabsorbed serum was diluted 1:2 with saline and each tested for agglutinins in amounts of 0.2, 0.1, 0.025 and 0.02 cc., corresponding to dilutions of 1:10, 1:20, 1:40, 1:80 and 1:100.

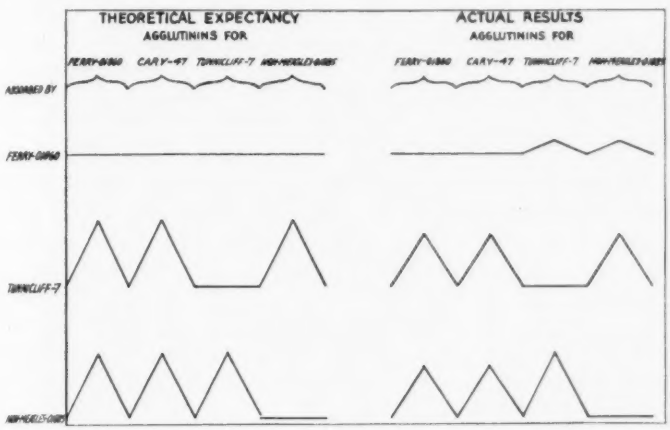
In table 13 are given the results with one of the serums, which is typical of the five tested.

Summary and Discussion of Agglutinin Absorption Experiments.—Ferry 01860 absorbed the agglutinins for Ferry 01860 and Cary 47, and almost completely absorbed the agglutinins for Tunnicliff 7 and nonmeasles streptococcus 01885.

Tunnicliff 7 removed the agglutinins for Tunnicliff 7 and slightly or not at all reduced the agglutinins for 01860, 47 and 01885.

Nonmeasles streptococcus 01885 removed the agglutinins for 01885, slightly reduced the agglutinins for 01860 and 47 and generally left them intact for Tunnicliff 7.

Assuming that the agglutinin-absorption test can be relied on for determining specificity and assuming also that the agglutinins found in the majority of the measles convalescent serums for Ferry 01860, Cary 47, Tunnicliff 7 and nonmeasles streptococcus 01885 are specific for Ferry 01860 and Cary 47 and are nonspecific or group agglutinins for the other two organisms, the theoretical conditions would be as follows: Ferry 01860 and Cary 47 would completely absorb the agglutinins for Ferry 01860, Cary 47, Tunnicliff 7, and nonmeasles 01885; Tunnicliff 7 would completely absorb agglutinins for 7 but not for 01860, 47 and 01885; and 01885 would completely absorb agglutinins for 01885 and not for 01860, 47 and 7.



Results with agglutinin absorption experiment with measles convalescent serums.

As a matter of fact, the actual results approached closely the theoretical expectancy, as may be seen in table 13 and also in the accompanying chart, in which the results are shown graphically.

In the chart, the bottom of the curve, or the horizontal line, represents complete absorption, while the tip of the curve represents the limits of the agglutination titers.

SUMMARY AND COMMENT

From the results of this work it seems apparent that the green-producing micrococci, described by the several authors quoted, are not similar.

Morphologically, culturally and serologically *Streptococcus morbilli* strains are identical.

Cary 47 agrees in every respect with *Streptococcus morbilli*.

The two cultures from Park, designated as R 83 and "Tunnicliff," are essentially alike.

The three cultures from Hibbard and Duval are alike and agree with the two Park cultures.

No two of the strains received from Tunnicliff are alike.

Throat 2 from Tunnicliff agrees with the Park cultures and the three Hibbard and Duval cultures.

When the straight agglutination test does not differentiate these green-producing micrococci, the agglutinin-absorption test can be relied on.

Complement-fixation results run about parallel with the straight agglutination results and are no more specific.

Of eighty-three measles convalescent serums studied, the large majority (88.5 per cent) agglutinated the Ferry and Cary cultures, while only a small proportion (9 per cent) showed any degree of agglutination with the Park-"Tunnicliff" and Hibbard and Duval cultures, and these only in the lowest dilutions of the serum tested.

Evidence, therefore, has hereby been produced, contrary to some opinions previously expressed in the literature, to the effect that the various green-producing micrococci obtained from measles included in this study are not all similar; in fact, there is such a wide variation between some of them that they do not compare morphologically, culturally or serologically.

It is apparent also that if all of these organisms sponsored by the several authors mentioned in this paper, are related to measles, in an etiologic capacity, it must be as a more or less heterogeneous group composed of several distinct types.

Book Reviews

Ueber das Problem der bösartigen Geschwülste — eine experimentelle und theoretische Untersuchung. Von Prof. Dr. Lothar Heidenhain. Paper. Price, 28 marks. Pp. 153, with 141 illustrations. Berlin: Julius Springer, 1928.

The author's working hypothesis that malignant tumors arise from an infectious origin was developed during forty years of surgical experience. During the past four years he has submitted it to an experimental analysis. About 2,400 white mice received injections of autolysates of certain closed carcinomas and sarcomas of human origin. The methods used in preparing the autolysates and making the injections are fully given. A 10 per cent suspension of fresh tumor substance in normal physiologic sodium chloride solution was also inoculated. Certain of the mice likewise were inoculated with tumors of animal origin. About 6 or 7 per cent of the inoculated mice developed neoplasms, which were studied.

The extensive experimental work is carefully and rather completely presented. It is splendidly illustrated; the numerous figures themselves are a real contribution to the study of cancer.

There cannot be any doubt that the tumors are real neoplasms. Heidenhain concludes that white mice may be successfully inoculated with various autolysates of human and animal carcinomas and sarcomas. A considerable number of the mice developed sarcomas after inoculation with carcinomatous autolysate and vice versa. As a consequence, the author concludes that the actuating influence, the "Erreger" or "Agens," is the same for both carcinoma and sarcoma. The neoplasms do not develop at the site of inoculation but in some distant region. Clinically and pathologically, they are essentially similar to those in man. Thus in spite of the position taken by most pathologists, particularly that adopted at the meeting of the German Pathological Society in 1926, the author remains an ardent advocate of the theory of infection.

Of major importance in the evaluation of results secured by Heidenhain is the question of the origin of spontaneous tumors in white mice. The tumors reported appeared in from three and one-half months to twenty-five months, usually about a year after the inoculation. The results would be more convincing had the tumors appeared in cancer-free strains such as those developed by Maude Slye. Differences in interpretation of the thoroughly presented data, however, do not detract from the general excellence of the monograph, which should prove of especial interest and value to students of cancer research.

Medicine Monographs, Volume XIV: Epilepsy. By William G. Lennox, Assistant in Medicine, Research Fellow in Neuropathology, Harvard Medical School and Stanley Cobb Bullard, Professor of Neuropathology, Harvard Medical School. Price, $3.50. Pp. 197. Baltimore: Williams & Wilkins Company, 1928.

This monograph, dedicated to William N. Bullard, is not an ordinary treatise on the "disease" epilepsy, but a comprehensive analytic study of the factors involved in convulsions in general. In fact, the authors maintain that our knowledge does not permit us to designate any convulsive state as "idiopathic" or "essential" epilepsy. There is no constant anatomic lesion in epilepsy, and only a minority of patients with extensive cerebral pathologic changes have fits. The authors accept the evidence adduced in favor of vasomotor control of the cerebral vessels as conclusive and lay some stress on signs of instability of the sympathetic nervous system in epilepsy. They hail as the greatest recent advance the demonstration that changes in physiochemical processes may modify seizures

profoundly. Paraphrasing the famous statement of Hippocrates that anyone who can render a man humid and dry, and hot and cold by regimen can cure epilepsy, they say: "Whoever is acquainted with physiology and can render a man acidotic, dehydrated and fully oxygenated can also repress this disease, without minding purification of narcisistic personalities, ritualistic imperial diets and all other illiberal practices of a like kind." Alkalosis and anoxemia are considered of importance as convulsive factors, while acidosis often is beneficial whether induced by rebreathing, ketosis or the administration of acids or acid-forming salts. Any person interested in scientific medicine will enjoy this book.

MODERN MEDICINE: ITS THEORY AND PRACTICE. VOLUME VI: DISEASES OF THE NERVOUS SYSTEMS, AND DISEASES AND ABNORMALITIES OF THE MIND. Original Contributions. By American and Foreign Authors. Edited by Sir William Osler, Bart, M.D., F.R.S., Late Regius Professor of Medicine in Oxford University. Third Edition. Reedited by Thomas McCrae, M.D., Professor of Medicine in the Jefferson Medical College, Assisted by Elmer H. Funk, M.D., Clinical Professor of Medicine, Jefferson Medical College. Price, $54 a set, $9 a copy. Philadelphia: Lea & Febiger, 1928.

The sixth and last volume of the revised edition of Osler's "Modern Medicine" is devoted to diseases of the nervous system and abnormalities of the mind. The twenty-one contributors include men who are well known in the field of Medicine in both America and England, and each of whom is an authority on his subject. Among these are Lewellys, F. Barker, Joseph Collins, Harvey Cushing and J. Ramsay Hunt. The introductory chapter on diseases of the nervous system by Barker should prove valuable to the general practitioner. He discusses the symptoms and physical observations of nervous disorders in general, discussing the physiologic background and diagnostic significance of such phenomena. Thereafter each of the major diseases of the nervous system is analyzed completely and authoritatively by the various contributors. The part by Edward A. Strecker, devoted to the diseases and abnormalities of the mind, emphasizes the importance of psychiatry in general medicine. He simplifies existing classifications and points out the significant manifestations presented by patients, in such a manner as to make them readily understandable to others than specialists in this field. On the whole, the third edition of this work succeeds in keeping Osler's Modern Medicine in the front rank of systems in medicine.

SYPHILIS, A TREATISE ON ETIOLOGY, PATHOLOGY, SYMPTOMATOLOGY, DIAGNOSIS, PROPHYLAXIS AND TREATMENT. By HENRY H. HAZEN. Price, $4. Pp. 643, with 165 illustrations, including 16 figures in color. St. Louis: C. V. Mosby Company, 1928.

This conveniently sized work contains an amazing amount of material, and presents concisely every aspect of syphilis. It tends to be a compilation, and other authors have written a few chapters. The text is well illustrated by photographs, photomicrographs and colored plates. Many of the legends preach unforgettable sermons.

The text is valuable in enabling students and practitioners to obtain a bird's-eye view of the disease and become familiar with general principles. The most valuable feature is that of diagnosis, which is incorporated throughout the early chapters and not confined to the one so designated. Syphilis in the negro is discussed.

The size of the text would permit, and its value would be enhanced by inclusion of more of the refinements of syphilologic practice. Individualization of patients for treatment and more detailed study of contraindications to and complications of therapy are of such great practical importance that more space could be devoted to them.

MÉTABOLISME CELLULAIRE ET MÉTABOLISME DES TUMEURS. OTTO WARBURG. Translated by E. Aubel and L. Genevois. Price, 30 francs. Paris: Félix Alcan, 1928.

This is not an exact translation of Warburg's "Stoffwechsel der Tumoren" published in Berlin in 1926, but it includes some of his more recent publications, and thus brings his work in its most recent state before the French-reading public. On the whole, the work is highly technical, dealing with the methods used by Warburg in his work on the metabolism of tissues, and with the results obtained by the study of various tissues, especially cancer tissue. The work, thus, is of interest chiefly to the biologist interested in the fundamental problems of the oxidation of tissues, and to the investigator in the field of cancer.

Two chapters of more general interest incorporated within the present volumes are: "The Metabolism of the Cancer Cell" and "The Present State of the Problem of Cancer." As Warburg's epoch-making work is not yet available in English, this translation may bring his methods, results, conclusions and speculations within the reach of a new group of readers.

EPILEPSY. By WILLIAM G. LENNOX, Assistant in Medicine, Harvard Medical School, and STANLEY COBB, Bullard Professor of Neuropathology, Harvard Medical School. Medicine Monographs, Volume XIV. Cloth. Price, $3.50. Pp. 197, with 14 illustrations. Baltimore: Williams & Wilkins Company, 1928.

This is a valuable and fascinating study of the factors involved in convulsions in general. The authors, who have done important investigative work in this field, also prove themselves equipped with a thorough grasp of old and recent research work in physiology, chemistry and pathology which has a bearing on this problem. While cautious in drawing conclusions and not at all ready to offer a solution to the riddle of epilepsy, they lay greater emphasis on chemical factors, such as alkalosis and "oxygen lack," and on disordered sympathetic nerve function and arterial spasm, than on the meager and inconstant information given by microscopic examination. Their reasoning leads them to discard the distinction between "idiopathic" and "symptomatic" epilepsy, as this implies a knowledge which we do not possess. However, they sound this hopeful note: "The encouraging feature is that, although the exact mechanism of seizures is unknown, much can be done to prevent and, in the early stages, to cure them. It is the duty of the physician to search out the various contributing or precipitating factors which, in the individual patient, may make for seizures. Correction of these abnormalities may effect sympathetic cure." The book can be highly recommended to the general medical reader as one that deals with a difficult subject in a clear, orderly and interesting manner.

CUSHNY'S PHARMACOLOGY AND THERAPEUTICS. By C. W. EDMUNDS, University of Michigan, and J. A. GUNN, University of Oxford. Ninth edition, revised. Cloth. Price, $6. Pp. 743. Philadelphia: Lea & Febiger, 1928.

Probably no textbook has played as important a part in the recognition and development of pharmacology in this country as has Cushny's. Workers in this field and in therapeutics will therefore welcome this latest edition, which has been revised and brought up to date by Edmunds and Gunn.

The general plan of the work has not been at all altered. The chief changes in the new edition are the insertion of the drug descriptions and dosages of the tenth United States Pharmacopeia, and alterations or extensions of the text to conform with progress in pharmacology and therapeutics. These changes have lengthened the book about thirty-six pages.

THE EXAMINATION OF PATIENTS. By NELLIS B. FOSTER, M.D., Associate Physician to the New York Hospital, Associate Professor of Medicine at Cornell University College of Medicine. Second edition, revised. Price, $4.50. Pp. 371, with numerous charts, plates and index. Philadelphia: W. B. Saunders Company, 1928.

In revising this well known book for its second edition the author has dealt briefly with the differential diagnosis of the more important diseases. Paragraphs on symptomatology are appropriately interspersed with those on systematic or regional examination. A whole chapter on the febrile diseases has been added. The diagnostic laboratory procedures have been brought up to date.

For a small manual it contains a wealth of valuable information and could profitably be kept on the study table of every senior student and intern.

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